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ON THE ALLEGED SYNCHRONIZATION OF PROPRIOCEPTIVE IMPULSES WITHIN SPINAL GANGLIA

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(Received for publication May 29, 1941)

KAYSER has recently compared the spike potentials of proprioceptive sensory fibers in the frog's sciatic nerve and in the 9th dorsal root when the gastrocnemius muscle is stretched. He reports a lower frequency and a higher voltage of the spikes in the dorsal root than in the nerve. These observations led him to the conclusion that "impulses produced by stretching a muscle running separately and irregularly within the nerve, become transformed in the spinal ganglion into synchronized and rhythmic waves of impulses" (Kayser, 1939, p. 504). It seemed worth while to test these conclusions experimentally, since synchronization of impulses is an outstanding problem in the physiology of the nervous system.

RESULTS

Procedure (Part 1). If synchronization of impulses actually occurs within the spinal ganglion, impulses starting at slightly different times in two proprioceptive fibers emerging from a single muscle might appear in the dorsal root as fused into a single spike. Therefore in a series of experiments in five bullfrogs we dissected out the sciatic nerve with the 8th and the 9th dorsal roots and with two branches of the medial popliteal nerve from the gastrocnemius muscle. The branches, put on separate electrodes in a moist chamber, were stimulated individually by induction shocks, the interval between which was regulated by a Lucas pendulum opening the primary circuits of two Harvard coils. Dorsal root potentials were recorded on the cathode ray oscillograph when the two nerves were stimulated separately and then together at various intervals in steps of 0.11 msec.

At only *one* setting of the movable key in each experiment did the spike appear truly single. The difference between the lengths of the two nerves (and perhaps a slight difference in conduction velocities) was sufficient to account for the fact that a single spike was seen in the root *not* when the stimuli were synchronous, but when they were separated by a definite small interval. An increment of only ± 0.11 msec. to this interval between the stimuli resulted in a change in the shape of the spike potential in the dorsal root. It therefore appears that synchronization did not take place.

Figure 1 shows the results of such an experiment. *B* and *C* represent records of the spikes in the dorsal root when the proprioceptive fibers in the two nerve branches were stimulated separately. *A* shows four composite spike potentials observed when the two nerves were excited with varying time intervals between the two stimuli. The summit of the composite spike is markedly delayed when the two impulses are separated by an interval of 0.22 msec., at an interval of 0.44 msec. the crests of the spikes begin to separate, and at an interval of 0.55 msec. they are quite clearly separated. The four curves in Fig. 1*D* were calculated from *B* and *C* by adding the ordinates of the curves in *B* and *C* with the peaks coincident and separated by intervals

of 0.22, 0.44 and 0.55 msec. The calculated curves in *D* agree closely with the summated spikes in *A* which were actually registered.

All five experiments agreed in showing that spike potentials reaching the spinal ganglion by way of different fibers do not become synchronized even when separated by intervals of only a few tenths of a millisecond.

Procedure (*Part 2*). To detect the mistakes that had led to Kayser's statements we repeated his experiments. In one bullfrog and 9 leopard frogs the gastrocnemius muscle was dissected out with the sciatic nerve and the lower end of the spinal column containing the ligated 8th and 9th dorsal roots. The preparation was mounted in a moist chamber with a clamp fixing the distal end of the femur, the nerve and one of the roots were placed on silver electrodes, and different weights were loaded on the muscle by a string passing over a wheel and attached to the tendon.

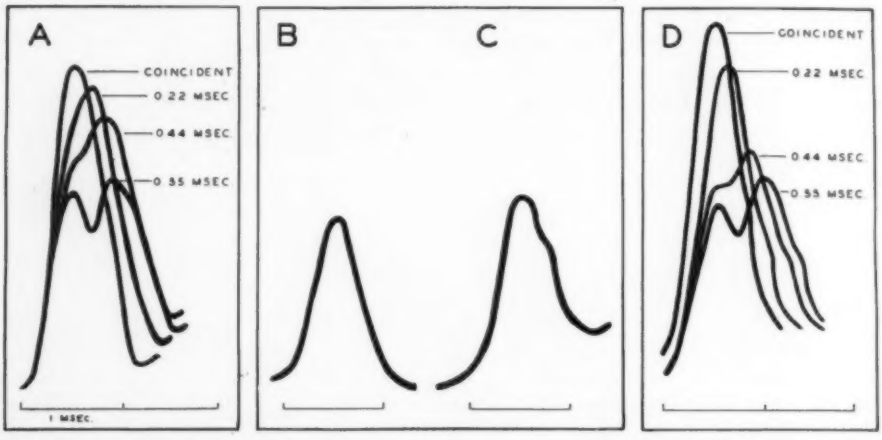

FIG. 1. "Coincident" means coincidence of spike potentials in the dorsal root, not coincidence of stimuli and the intervals represent increments of interval between stimuli, not absolute intervals. *A*, Spikes recorded from the 9th dorsal root when two muscular branches of the medial popliteal nerve were stimulated at intervals as indicated. (The intervals are accurate to within ±0.05 msec.) *B* and *C*, Spikes recorded in the same way when each branch was stimulated separately. *D*, Calculated summation of spikes *B* and *C* at same intervals as in *A*. (Bullfrog 12/20/40.)

Even when the muscle was loaded with weights of only 10 to 50 g. the proprioceptive impulses recorded from the nerve were so many and occurred at such irregular intervals that it was not possible to identify the potentials coming from single fibers. Typical monophasic recordings of the activity in the nerve immediately upon loading the muscle are given in Fig. 2*A* and 3*B*. Figures 3*C* and 3*D* are from similar experiments, recorded diphasically. As is to be expected, the spikes are much higher in the monophasic recordings than in the diphasic. The highest spikes in these records are probably all chance summations due to transient synchronies.

In monophasic records from the dorsal roots it was often possible to identify the activity of single fibers (Fig. 3*A* and 4*B*). Figure 4*B* shows the potentials recorded from the 8th root of a leopard frog 0.5 sec. after loading the gastrocnemius with 20 g. Besides a few relatively small and irregular re-

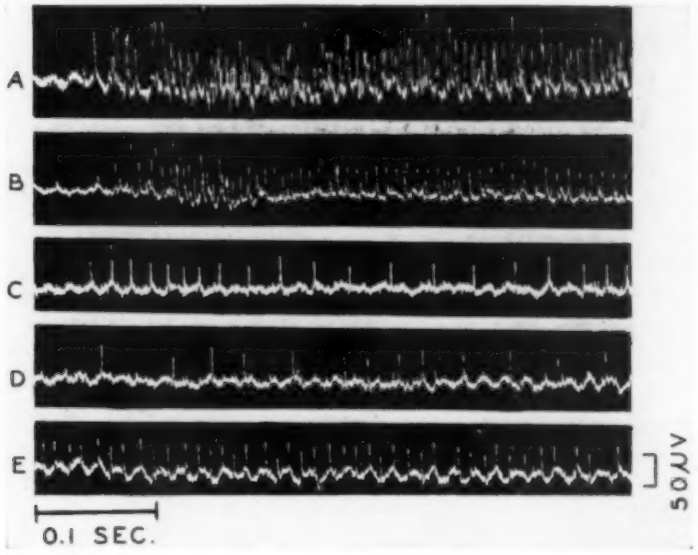

FIG. 2. *A*, *B*, *C* and *D*: Proprioceptive responses recorded monophasically when gastrocnemius was stretched. *A*, from sciatic nerve, weight 50 g.; *B*, from 9th dorsal root, weight 50 g.; *C*, same as in *B* 30 min. later; *D*, from 9th root, weight 10 g. *E*. Spontaneous firing of a single receptor, 9th root (frequency 92 per sec.). Such spontaneous firing was rare in our experiments. (Leopard frog 5/6/41.)

sponses there are two series of spikes occurring at fairly regular intervals at frequencies of 58 and 64 per sec. The first and the last high spikes of this series consist of the two coincident impulses, whereas all those between them

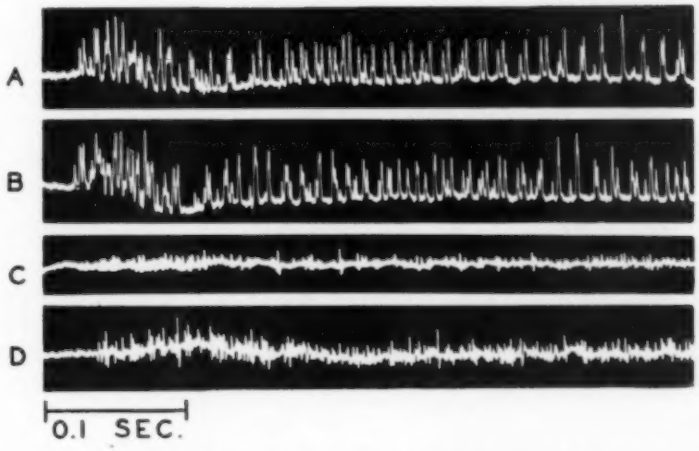

FIG. 3. Activity of proprioceptive fibers elicited by stretching gastrocnemius muscle with 20 g. (3/5/41). *A*, Recorded monophasically from 8th dorsal root. *B*, Recorded monophasically from sciatic nerve. *C* and *D*, Recorded diphasically from sciatic nerve. Amplification in *D* twice that in *A*, *B* and *C*.

are distinctly separated. Even in the potential before the last, two distinct spikes are clearly distinguishable.

Activity limited to only *one* fiber was occasionally encountered (Fig. 2*B*, *C*, *D*). In Fig. 2*C* the frequency, initially 68 per sec., dropped to about 30 after a quarter of a second; later it rose again to its initial value. This secondary increase in frequency is similar to the second increase observed by Hartline (1935) in the responses of a single fiber from the eye of *Limulus*.

Generally more frequent and higher summated spikes were found in the nerve than in the root (cf. Fig. 2*A* and *B*). In a few cases the potentials in the nerve and in the root looked very much alike (Fig. 3*A* and *B*). Since in this frog the 9th root also showed responses very much the same as those represented here, the similarity of *A* and *B* certainly cannot be explained by assuming that most of the proprioceptive fibers active in the nerve entered the 8th dorsal root. Furthermore, spikes recorded monophasically were never found to be larger in one of the roots than they were in the sciatic nerve.

Discussion

Synchronization of active neurons has often been encountered in the central nervous system and to some extent also in peripheral nerves. Adrian (1930) describes synchronization of spontaneously discharging fibers in excised mammalian nerves. "The most reasonable explanation seems to be that an active fiber can cause a slight momentary increase in the stimulus to other fibers and that it can do so owing to the action current which it produces." Such a synchronization may occur if fibers are exposed to a *constant* stimulus, *e.g.*, at the injured ends of the nerve fibers, but Adrian's explanation of course would not hold for a synchronization of fibers each of which responds to a different rhythm imposed on it by its peripheral end-organ. In crab nerve fibers Katz and Schmitt (1939) reported a synchronization and equilization of speed of impulses when an impulse in one fiber slightly precedes that in an adjacent fiber. They explain the phenomenon as due to a reduction of the propagation velocity by an interference of the local action potentials.

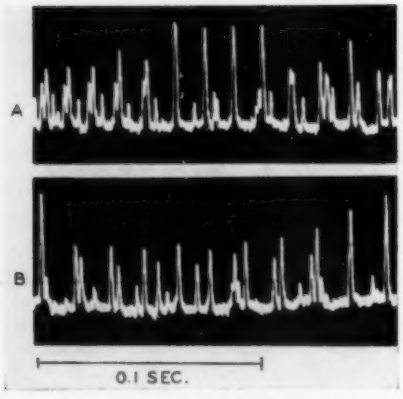

Fig. 4. *A*, Responses from several fibers, two of which become almost synchronized for about 0.05 sec., recorded from sciatic nerve. *B*, Two fibers active at slightly different frequencies (64 and 58 per sec.), recorded from 8th dorsal root. (Leopard frog 3/5/41.)

Kayser inferred a synchronization of impulses within the spinal ganglion mainly because (i) he had recorded larger spikes from the 9th root than from the nerve and (ii) there were fewer spikes in the root per unit time than in the nerve. The difference in size was to be expected, since the potentials in

the root were recorded monophasically (cf. Kayser, 1939, Fig. 1), those in the nerve diphasically.* Also, fewer spikes are to be expected in the 9th root than in the nerve because part of the proprioceptive fibers active in the nerve reach the spinal cord through the 8th and perhaps the 10th roots. Furthermore some of the fibers in the root may sometimes be damaged in preparation or may deteriorate during the experiment.

It is true that transient synchronization may occur from time to time (Fig. 4*A*), but it is rarely maintained for more than one or two impulses (Fig. 4*B*). Kayser believed that the large spikes that he recorded from the root were the summations of many impulses, but their fairly constant height, regular rhythm and gradually decreasing frequency are highly characteristic of the responses of a *single* receptor.

Summary

No synchronization by the spinal ganglion was apparent when two discrete sets of proprioceptive fibers were stimulated with intervals of a few tenths of a millisecond between the two electric stimuli. Experiments in which proprioceptive fibers were stimulated by stretching the gastrocnemius indicated that there was no synchronization because

1. *Monophasically* recorded spikes were never larger in the dorsal roots than in the sciatic nerve.

2. Typical recordings from the dorsal roots contained two or more simultaneous regular trains of impulses occurring at slightly different frequencies.

3. Responses of equal height occurring at a constant frequency or at intervals that slowly increase with time (adaptation) are characteristic of single-fiber activity. No evidence of a regular continuing sequence of *composite* spikes was found.

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*The excursions of his spikes below the baseline in his recordings from the roots (cf. Fig. 2 and 5) are due to incomplete damping of the string, as is indicated also by the later oscillations.

HYPERACTIVITY IN MONKEYS FOLLOWING LESIONS OF THE FRONTAL LOBES*

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(Received for publication July 3, 1941)

INTRODUCTION

BILATERAL ablation of the frontal lobes of monkeys is followed by a marked hyperactivity which is characteristic of this lesion. Such animals display a "drivenness" of motor performance reminiscent of the incessant pacing of a caged lion, being characteristically purposeless, repetitive and seemingly interminable.

A spontaneous increase in activity resulting from lesions of the frontal lobes has been reported previously in many animals. In man, bilateral frontal ablation is followed by distractibility, easy excitability and sometimes by overactivity (Brickner 4, Levin 14, Hebb and Penfield 7). Increased irritability is also associated with frontal lobe pathology, as in "behavior problem" children (Levin 14).

In *dogs* and *monkeys* the syndrome of hyperactivity has been described by Ferrier (6) and Bianchi (3); in monkeys by Jacobsen (9); in cats by Langworthy and Richter (12) and Magoun and Ranson (15); and in rats by Lashley (13). It was quantitatively measured by Richter and Hines (16) in monkeys, and by Richter and Hawkes (17) in rats. Increased activity following bilateral removal of area 8 alone (as well as after ablation of the entire frontal association areas, *i.e.* areas 9–12 of Brodmann) has been noted in monkeys (Kennard and Ectors 11), and Richter and Hines (16) believe that the increased activity after frontal ablation is further augmented when the caudate nucleus is injured. Beach (1, 2), however, does not find markedly increased activity after frontal ablations or caudate injury in rats.

Many of the observations on increased activity have been described casually as part of the syndrome of frontal lobe ablation. In man, "drivenness" and hyperactivity have been difficult to analyze, from either the point of view of the cause or nature of the symptom. The papers of Richter and Hines and of Beach are perhaps the only ones dealing primarily with activity changes, and their results are not in accord. Richter and Hines have attempted further systematic analysis. In this laboratory also spontaneous increase in activity peculiar to extirpations of the tips of the frontal lobes was first observed casually (Jacobsen 9; see also Kennard and Ectors 11, Kennard 10), but during the past 5 years more systematic and intensive analysis has been attempted. The results are summarized in the present paper.

* Aided by a grant from the Knight Fund, Yale University School of Medicine.

METHOD

Monkeys have been used, either *Macaca mulatta*, or the sooty mangabey (*Cercocebus torquatus atys*). Activity was measured both before and after operative removal of various portions of the central nervous system by means of kymograph records taken over a two-hour period in which the animal was allowed to move at will in an oblong cage 4 ft. ×1.25 ft., and 1.25 ft. high. The floor of this cage consisted of a galvanized iron pan which was set upon two pneumatic pads one at each end. These were slightly inflated with air and connected directly with a Marey tambour recording on the the kymograph with ink. Thus, movement of the animal resulted in a stroke of the pen and number of strokes equalled roughly the amount of activity. Since the pre- and postoperative differences between amounts of activity were very great, the method was sufficiently accurate (Fig. 1). In many instances a numerical count of strokes was made, but for the remainder records were rated as of low, medium or high normal activity, or of low, medium or high hyperactivity.

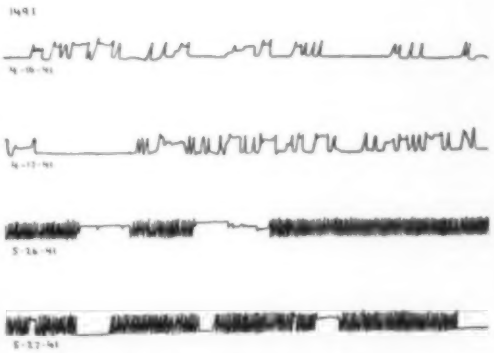

FIG. 1. Changes in activity as result of bilateral ablation of areas 8–12 on April 29, 1940.

Various control conditions were maintained but routine tests were made in the morning with the animals fasting under conditions as quiet as possible. The lights were kept on to insure uniform illumination. Other tests were carried out in a dark and soundproof room, and still others with varying degrees of light. The effect of both prolonged fast and of over-feeding were also tried.

DATA

Nature of hyperactivity. A normal monkey, placed in the oblong cage just described, exhibits a variety of behavior depending on its nature and the stimuli of the moment. Thus a two-hour record of such activity may vary moderately, but total activity seen on records made on 3 successive days is fairly uniform. There is considerable variation between individual animals, but in 53 normal animals hyperactivity approximating that in animals after lesions of the frontal areas has been encountered in only 3 instances. Those three monkeys were discarded from the series and no explanation was found for the high level of activity.

Frontal lobe hyperactivity is so typical that the animals may be picked out from a room full of other monkeys by the character of their cage performance. They move constantly back and forth and up and down from the perches. Movement is conspicuously purposeless and repetitive, although its pattern is often too complex to be called perseverative. Such animals, when fed, may be obviously hungry yet moving so fast that they cannot eat. They will pick up bits of food, jump upon the perch, take a bite, put the food down, grab it again and repeat the performance indefinitely. Their easy distractability is noticeable at all times. Stimuli evoke a greater response than in the normal animal, and emotional stress always increases activity. Otherwise, their personalities remain unchanged, they are neither more irritable nor more pleasant, more curious nor more fearful than before operation. A cer-

tain lack of discrimination seems also to be present. Any object may be put into the mouth, and the animal may attempt many times to reach something well outside the bars of the cage; the purposelessness of the hyperactivity thus indicates lack of appreciation of environment.

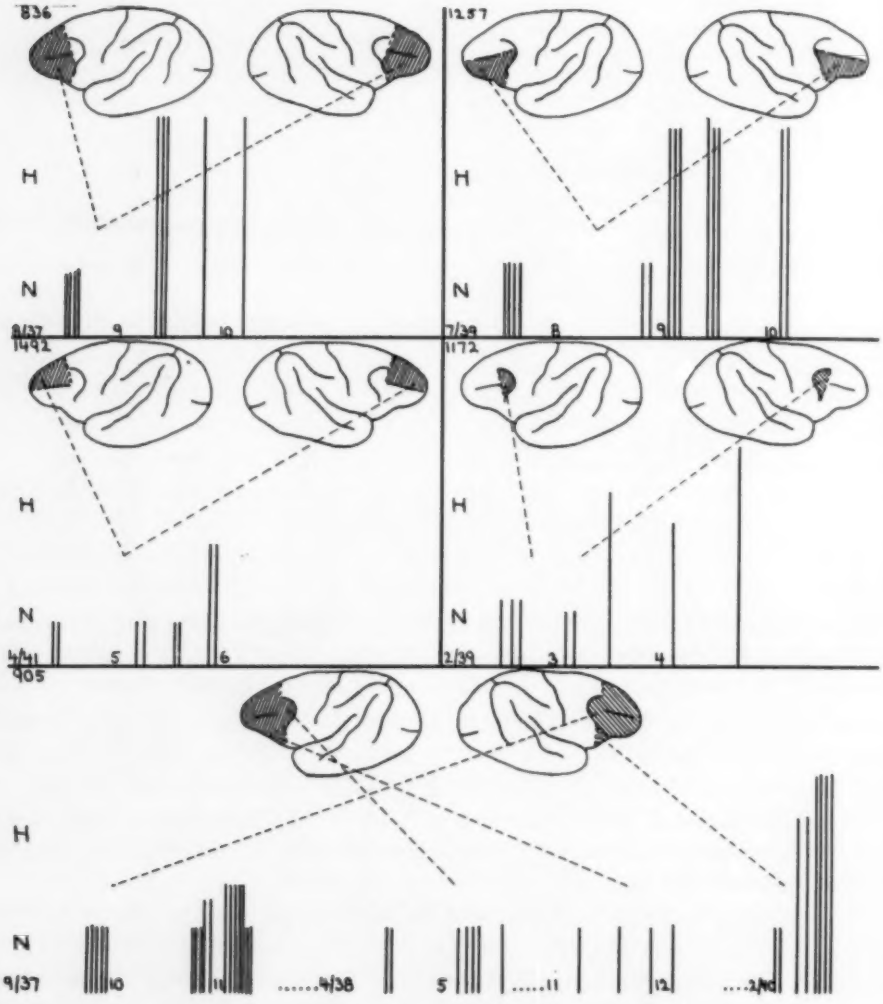

FIG. 2. Effect on activity of various bilateral lesions of frontal lobes. N = normal and H = hyperactive range of activity. Time in months indicated by figures on baselines. Time of operation shown by dotted lines connecting sketch with activity record.

The hyperactivity is usually preceded by a period of hypoactivity immediately following the operation which may last a few days or weeks. During this time, the animals appear confused, lethargic, slow and difficult to rouse. They often have to be fed by force since they show no interest in food or other objects. This is not a manifestation of the so-called postoperative

shock, for it is specific to lesions of the frontal lobes and does not occur following bilateral lesions elsewhere. Also, in many instances it lasts much longer than does the immediate effect of the operation.

2. *Localization within cerebral cortex.* Hyperactivity of this sort appears only after ablations from the frontal lobes. It occurred most rapidly and in greatest degree in 12 monkeys which had bilateral ablation of areas 8–12 (Fig. 2). Bilateral ablations of areas 9–12 also produced particularly marked hyperactivity in five animals. Removal of area 8 from both sides produced hyperactivity in 6 cases. For some days these monkeys all showed other symptoms of removal of area 8, *i.e.,* limited conjugate deviation of the eyes, a mask-like face and fixed gaze together with a marked slowness in all movement. But after removal of area 8 alone the increase in activity was never as great as that which followed removal of the larger areas; and, when at a second operation, areas 9–12 were added to the ablations of area 8, total activity again increased.

Removal of area 9 bilaterally in 3 cases was followed by a slight increase in one instance, but no increase in the other 2 cases (Fig. 2). In contrast, removal of the lateral portions of the frontal association areas, areas 8, 10, 11 and 12 without area 9 in 4 cases had the effect of increasing activity much more markedly. The subsequent removal of the remaining portions of the frontal lobes increased activity again in both cases.

Involvement of the caudate head or of the putamen seemed in our cases to have no effect on the amount of activity. It was undamaged in the majority of cases after bilateral removal of areas 9–12 in which hyperactivity was extreme, although it was injured in some instances. Moreover, when the caudate head alone was removed bilaterally via a mid-line approach and section of the corpus callosum, there was no increased activity.

In our experience, *unilateral* ablation of any of these cortical areas has had slight effect on activity. In only 3 cases out of 11 in which activity has been measured before and after unilateral ablation of frontal association areas has hyperactivity appeared, and in these 3 cases it was slight, and it increased greatly when the opposite area was later amputated.

Effect of other cortical lesions on hyperactivity induced by lesions of frontal association areas. Bilateral extirpations from parietal or temporal lobes do not produce hyperactivity. Bilateral removal of area 6 is followed by transient hypomotility which is most marked when the lesions have been simultaneous on the two sides. With recovery from this, however, there is no hyperactivity. Moreover, no lesion or combination of lesions made subsequently in other parts of the cortex will diminish the hyperactivity which has appeared after lesions of frontal association areas, unless such profound paresis develops that the movement of the animal is interfered with, or unless vision is sufficiently restricted, by occipital lobectomy.

In one monkey when all of one hemisphere had been taken out, together with areas 8–12 on the other side, hyperactivity occurred. In another, from one hemisphere areas 9–12; areas 6, 4, 3, 1, and 2; and areas 17 and 18 were

removed in three successive operations in that order. No hyperactivity resulted but at a 4th operation in which the remaining areas 9–12 were extirpated, hyperactivity became marked. A third monkey had the left frontal lobe and area 8 of the opposite side extirpated. Hyperactivity followed. Then area 6 was removed without altering activity although temporary partial paresis occurred. Finally, when the remaining area 4 was extirpated marked paresis appeared and hyperactivity consequently became impossible.

Factors affecting hyperactivity. (a) *Sound.* Since the animals were noticeably distractible the effect of removal of distraction was tried. The activity cage was placed in a sound proof room. Records there showed no diminution in activity, but rather a slight increase, for greater regularity of movement was present obviously due to the fact that there were none of the momentary pauses which usually appeared because of distraction by some slight sound. In one monkey, activity was normal after section of both eighth nerves. Subsequent ablation of both frontal association areas then produced hyperactivity.

(b) *Light.* Whenever a hyperactive monkey was placed in the dark, all activity ceased. This occurs also in normal monkeys and might be expected since their tree-dwelling habits require light for safety in movement. It seems more remarkable, however, in the hyperactive animal. Two monkeys from which the eyes had been enucleated had all of areas 8–12 removed, one before and the other after enucleation. No hyperactivity resulted. A third animal was tested from which both occipital lobes had been removed in infancy and which was at the time of testing, nearly three years old. The pupils of this macaque responded definitely to light as is to be expected from the work of Marquis and Hilgard (16). In addition it would move its head and eyes to follow strong light, but no object vision further could be demonstrated. Its activity prior to ablation of the frontal areas was normal. Following their removal it became slightly more active, although true hyperactivity never appeared. A fourth animal was made hyperactive, and then had both occipital lobes removed. Hyperactivity ceased.

The effect of continued light was, as would be expected, the opposite of dark. Activity measured during the night if the lights were kept on remained high. One animal kept in the light for 48 hours continued to be hyperactive for this interval, although at the end of the period there were brief pauses during which it would lie down or sit, apparently because of fatigue, only to jump up again and resume pacing.

(c) *Hunger.* Since the frontal lobes are suspected of having direct effect on autonomic functions (8, 18, 19), increased metabolism or possibly increased hunger "drive" was a possible source of activity. Therefore monkeys were tested during fasting and overfed conditions. It was found that normal controls fed a fixed diet at a fixed time daily were slightly more active before feeding than during the hour immediately after. The same effect appeared in the hyperactive monkeys, but it could not be seen that hunger affected activity more in these than in the normal animals.

Metabolism. Since basal rates in monkeys are somewhat difficult to obtain (Bruhn 5), a series of animals was next placed on a weighed diet, before and after ablation of frontal association areas. Weight and intake were compared (Fig. 3). Again, no marked signs of increased metabolism were found

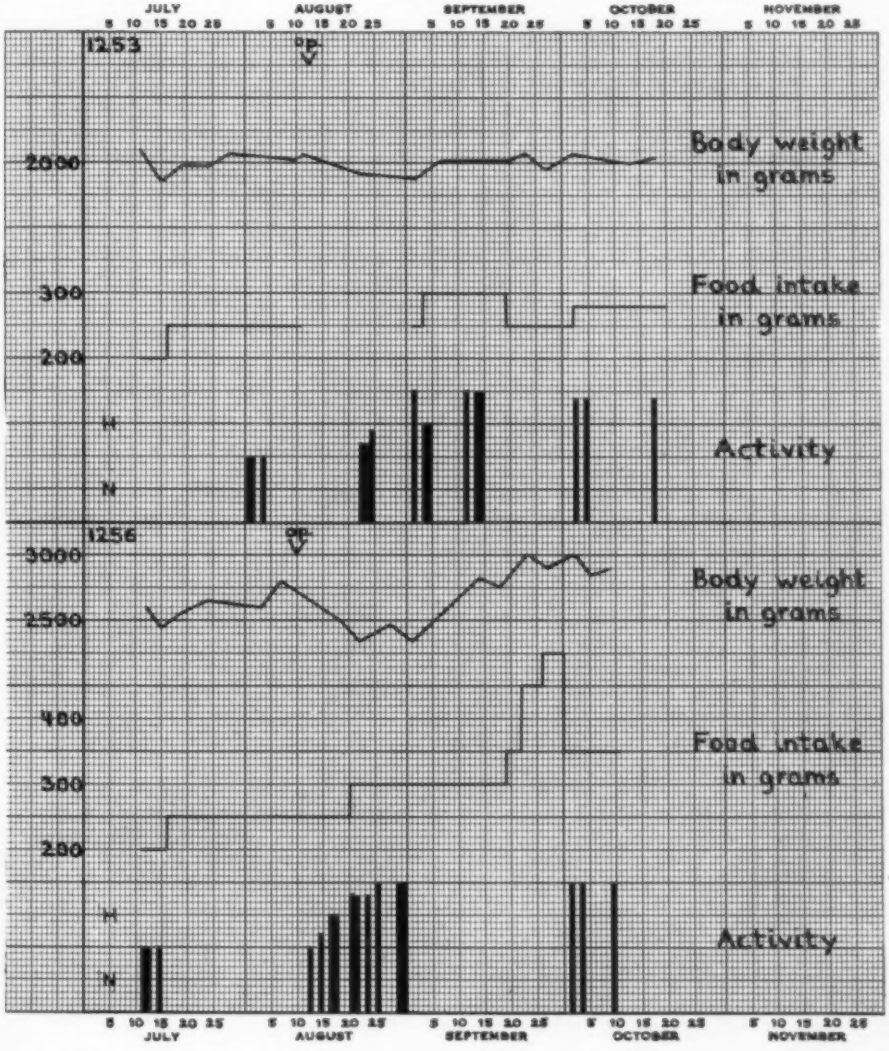

FIG. 3. Records of two *Macaca mulatta*, made hyperactive by removal of areas 8–12 during period of controlled feeding, no loss of body weight, although activity increased. Arrow marks time of operation. N = normal, and H = hyperactive range of activity.

following operation. The hyperactive animals gained weight slightly more slowly than the normal or required slightly more calories for equal weight gain with the normal, but no more than might be necessary for the increased work of increased activity, and far less than was necessary for hyperthyroid animals.

Five monkeys have been placed on daily thyroid dosage sufficient to increase their metabolic rate to marked degree. These were made hyperactive before or after thyroid dosage. The results of these investigations will be reported in detail at a later date when fully completed. Figure 4 shows the marked differences between hyperthyroid and hyperactive animals, which had totally opposite responses in almost every respect. On a weighed fixed diet hyperactive animals lost little weight, although activity increased enor-

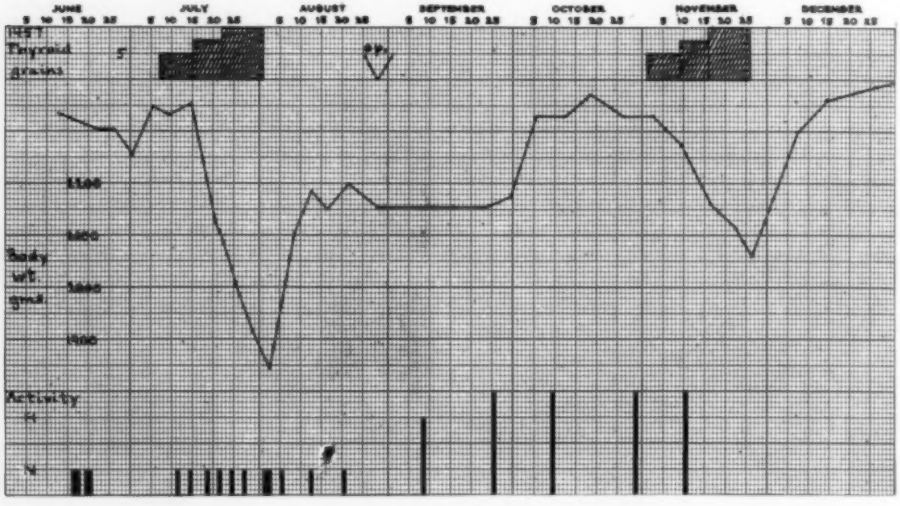

FIG. 4. Changes in body weight and activity, following ablation of areas 8–12 and during thyroid medication. Standard diet throughout experiment. N = normal, and H = hyperactive range of activity.

mously. Those with increased metabolism, on the other hand, lost weight rapidly, but increased activity but little (Fig. 6). Pulse and blood pressure rose significantly in hyperthyroidism but little if at all in hyperactivity. The gastrointestinal peristalsis was measured by means of carmine tablets which were given by mouth, the time being recorded when color appeared in the feces. Figure 5 indicates that the rate of peristalsis did not decrease during hyperactivity, but that it diminished from the normal of 18–24 hours to 2, 4, or 6 hours in the hyperthyroid monkeys. It seems certain therefore that neither increased metabolism nor changes in the autonomic functions of the gastrointestinal tract can be responsible for hyperactivity.

In the three species of monkeys operated upon (macaque, mangabey and cebus) all of which walk as quadrupeds, the pacing repetitive motion has been extreme. In the chimpanzee, which walks for the most part upright, and has a more complicated frontal lobe, there is a somewhat different response to bilateral frontal lobe ablations. Two such chimpanzees have been prepared in the laboratory. Both showed restlessness and distractability of sufficient

intensity to be noted independently by several observers. There was, however, little of the pacing restlessness of the quadrupedal primates.

Discussion

The surprising phenomenon of an enormous increase in activity appearing after injury to the frontal lobes in animals whose behavior is otherwise normal has been redemonstrated in this series of monkeys. The purposeless and repetitive elements of the hyperactivity, together with its "driven"

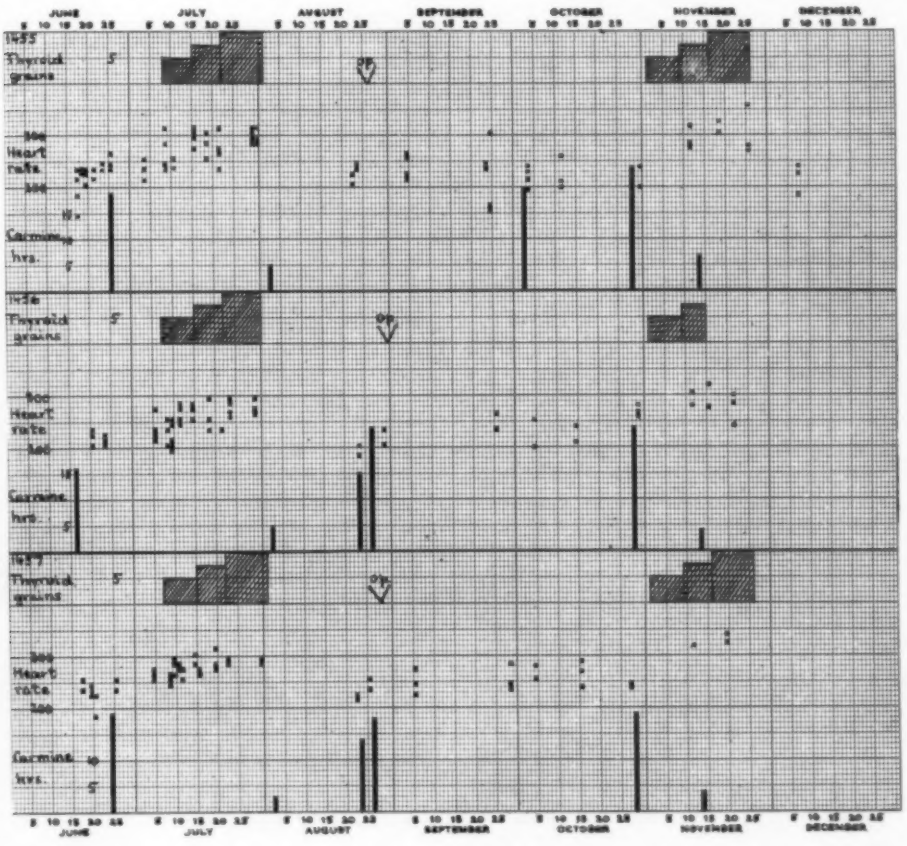

Fig. 5. Effect of thyroid on heart rate and intestinal peristalsis (passage of carmine through G. I. tract) before and after bilateral ablation of areas 8–12 in 3 *Macaca mulatta*.

character have been conspicuous as noted by all previous observers, but activity is so general an attribute that analysis of the factors effective in its production is difficult.

Our data, however, indicated that these alterations cannot be ascribed to changes in metabolism or to other autonomic disturbances, for no autonomic function was found affected. Furthermore a normal or a hyperactive monkey, when given thyroid, exhibits increase in blood pressure, heart rate and in-

testinal peristalsis, together with all the characteristics shown by hyperthyroidism in man, *i.e.*, loss of weight, increased appetite, nervousness, sweating and easy excitability, but activity will increase only slightly during hyperthyroidism.

Attempts to localize within the frontal association areas one region which

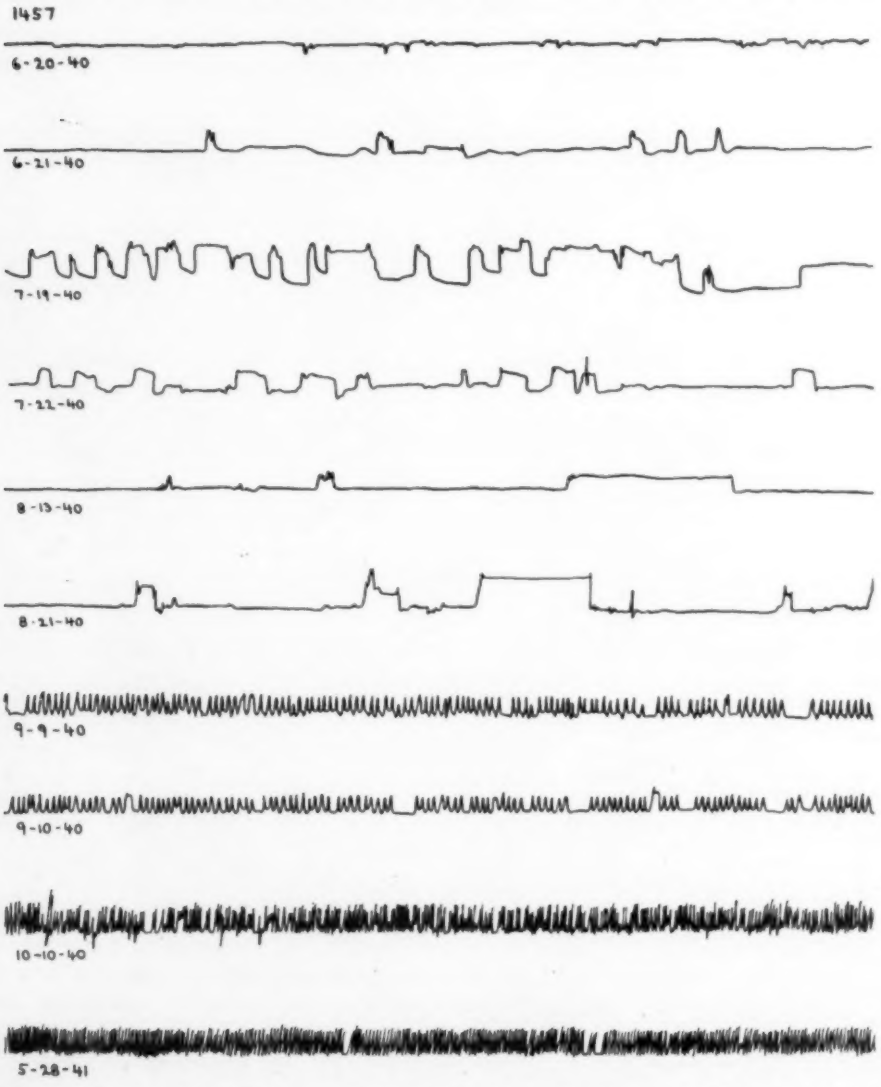

FIG. 6. Changes in activity as result of thyroid medication and bilateral ablation of areas 8–12 in a *Macaca mulatta*. Thyroid from July 7–31. Bilateral ablation of areas 8–12,—Aug. 29, 1940.

is responsible for hyperactivity have failed. Bilateral removal of the total area, or of all of it except area 8, undoubtedly causes greater activity and more quickly than do partial lesions. However, Richter and Hines have

found moderate increase in activity after removal of these areas from one side only; bilateral extirpation of area 8 alone causes marked hyperactivity, and ablations of fractions of areas 9–12 likewise increase activity moderately. If, however, one part is removed and at a later date the remainder extirpated, increased activity occurs after the second operation as well as after the first. The entire region seems thus to affect activity since removal of no part causes as great a change as does removal of the whole.

The lateral portions have more effect than do the mesial. The record of one animal is of interest in this connection. It can be seen from the chart (Fig. 2) that activity changed little in this instance after the first three operations, but that following a fourth which removed a final bit of the lateral tissue, a great increase in activity occurred.

What then can be the mechanism responsible for a change in total activity of an organism without other change in motor, sensory, or autonomic function, a change roughly proportional to the amount of tissue removed? The theory of "release of function" is inviting for it is used in relation to other functions of the frontal lobes such as postural regulation, for removal of specific portions of frontal lobes results in exaggeration of function; integration of the function in question can therefore be attributed to this area under normal conditions. These release mechanisms have another factor in common, which is the variability in time at which release becomes evident after the lesion has been made. Hyperactivity, hyperreflexia and spasticity appear at an unpredictable time following operation and there is nothing in the data which explains the time of appearance. Neither species nor age, as far as can be seen, affect hyperactivity, nor does the length of time under anesthetic, or the severity of the operation. Yet the hyperactivity may appear on the day after operation, or it may not be seen in full intensity until a month has passed. The intensely hyperactive animals do, however, show changes earlier than do those which are to become only moderately hyperactive. The same relationship to time appears in the "release phenomena" of reflex grasping or spasticity. There is as yet no valid theory to account for the temporal progression of this reorganization.

There remains one fact which may contribute to the causes of hyperactivity, namely that *it is altered by visual stimuli*, although auditory stimuli have no such obvious effect. When this work was in its early stages it was found that ablation of area 8 from one hemisphere produced inability to recognize objects in the contralateral field of vision, and that bilateral ablation of area 8 was followed by a temporary condition in which the monkey appeared dazed and showed no evidence of recognizing objects visually (10). It was thought that this might be a cause of hyperactivity and distractability. For, if objects were not recognized they might be ignored. There is still possibility that this, or a like mechanism affects activity, but it cannot be the whole cause since the failure to recognize objects is a transient affair, whereas hyperactivity is permanent and occurs when areas 9–12 have been removed without visual symptoms, if area 8 is undamaged. That areas 9–12 affect

vision to some extent is evident since although their removal causes neither conjugate deviation of the eyes nor failure to recognize objects seen, their ablation simultaneously with area 8 always results in increase in intensity and duration of these symptoms (11).

Jacobsen has shown (9) after bilateral ablation of the frontal association areas, that monkeys and chimpanzees lose their "immediate memory." They are unable to pick the correct inverted cup under which food has been placed in their sight if the field has been cut off from their vision for a short time afterward, although previous to operation they can make correct choice under such conditions. This loss of "delayed response" may be associated with the effect of light on activity as indicated by the subsequent work of Malmo (unpublished) who, substantiating Jacobsen's findings, has shown that if light is greatly cut down the monkey retains some ability to recall although it is limited when compared to preoperative performance. Both the hyperactive condition and the test situation of "immediate memory" are thus affected by visual stimuli, and distractability becomes directly proportional to light in both instances.

There are no data on the effect of visual stimuli on man without frontal association areas. But restlessness and distractability are recorded by many observers and discussed recently by Brickner (4). The compulsive behavior of the "behavior problem" may have a like background producing restlessness (Levin, 15).

The chimpanzee, now a familiar intermediary between man and monkey in the elucidation of problems of the central nervous system, has here proved a connecting link also. Man, monkey and the chimpanzee it is agreed, all show an exaggeration of the compulsive type of behavior when the frontal lobes are damaged. In all three, restlessness and distractability are increased. The monkey then walks on and on incessantly, but chimpanzee and man have more complex compulsive patterns. Increased activity can be found, but over-reaction to the stimuli inducing emotion and to those which require a knowledge of previous conditions are most conspicuously affected (Brickner, 4).

Experiments with the monkey and chimpanzee give information on another manifestation common in frontal lesions in man, namely the lethargy, or hypoactivity which is found with some frontal lobe lesions. Dullness, slowness, inertia or hypomotility are as often recorded as are restlessness or overactivity in these cases, and many times this cannot be due to generalized increased intracranial pressure.

In the monkey and chimpanzee hypomotility follows bilateral ablation of area 6 or temporarily of area 8. When the rostral portion of area 6 is removed paresis is slight but reflex grasping marked. Confusion and unresponsiveness to all types of stimuli are present, and perseveration is evident. In the monkey this will disappear in the course of a few weeks; in the chimpanzee it becomes less marked but lasts indefinitely. Transient symptoms of bilateral removal of area 8 are also confusion and hypomotility combined

with, and no doubt due to, a failure to recognize objects seen (10); a fixity of eyes and of facial expression adds to the impression of dull and unresponsive apathy.

It is therefore possible that in man also, hypomotility may be a manifestation of bilateral involvement of the frontal lobes in the regions of areas 6 and 8, whereas the restless driven patient may have destruction of more rostral regions which are relatively silent fields for physiological investigation, but which are more directly concerned with psychological properties.

Summary

1. In monkeys and chimpanzees ablations from the frontal association areas (areas 8–12 of Brodmann) result in increased total activity which is beyond that ever seen in the normal animal.

2. This hyperactivity is characterized by purposelessness and by repetitive continuation. It is permanent.

3. Partial ablations, if bilateral, produce some increase in activity (bilateral area 8, bilateral area 9, or bilateral areas 10–12), but none of these cause as great increase as does removal of all of the frontal association areas.

4. The increased activity has not been found to be related to increased hunger or metabolism; or to changes in the autonomic system.

5. Hyperactivity is markedly affected by visual stimuli. It disappears in the dark, or when the animals have been deprived of vision either by enucleation of the eyes or occipital lobectomy. Absence of auditory stimuli has not the same effect.

5. Hypomotility in monkeys and chimpanzees is related to lesions of the rostral portions of areas 6 and to area 8.

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THE SPINAL MECHANISM OF THE PYRAMIDAL SYSTEM IN CATS*

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IT IS THE purpose of this study to examine the functional organization of that portion of the spinal integrating mechanism which is subject to activation by the pyramidal system.† To this end it is imperative that other sites of integration be eliminated, and that pyramidal impulses alone be allowed to enter the spinal cord. Stimulation of the "motor" cortex may not be employed, because cortical facilitation will result (Graham Brown, 1915a; Adrian, 1936), and because of the inevitable participation of the extrapyramidal system in the distribution of activity to the spinal cord (Schäfer, 1910; Tower, 1936). Just as complete interruption of the pyramidal tracts without damage to other systems may only be accomplished by section of the pyramids in the medulla (Marshall, 1936), so only at the pyramids may the tract be stimulated without activation of other systems, and then only by the use of additional precautions. Other elements within the medulla, notably the reticular formation, may be activated by pyramidal collaterals or by direct extension of the stimulating current. The latter mode of activation has been known to occur even when electrodes designed to concentrate the stimulating current across the pyramids have been used. It has been necessary, therefore, to interrupt all pathways other than the pyramids at a level caudal to that of the stimulating electrodes. In consequence the preparations are essentially spinal, for conversion from the decerebrate state to the spinal state, in the cat, accompanies lesions of the vestibular nucleus or its direct pathway (Fulton, Liddell, and Rioch, 1930a, b).

It is not enough that pathways other than the pyramidal tract be interrupted below the site of the stimulating electrodes. A complete transection cranially is necessary to prevent ascending activity from reaching the cortex by various channels (antidromically along the pyramidal fibers, thence by collaterals, or dromically through the medial lemniscus and thalamus, etc.), there to activate pyramidal neurons. With all the foregoing precautions, the necessity for which has been shown by experience, the activity reaching the spinal cord as a result of a single pyramidal stimulus is a controlled single pyramidal volley.

Cats have been used throughout the present investigation. These were lightly narcotized with Dial or nembutal. Supplemental ether was regularly

* A preliminary account of some of the present results was presented at the meeting in Chicago of the American Physiological Society (Lloyd, 1941c).

† The definition of the pyramidal tract used herein follows from the descriptions of Türck (1851, 1853) and Flechsig (1876), *i.e.* the pyramidal tract consists of those fibers which pass through the pyramid to the spinal cord. For a discussion of the use of the term pyramidal tract cf. Marshall (1936).

used until the preparation was decerebrated or rendered essentially spinal. Most of the preparations made in this way were at the upper limit of irritability beyond which the present type of experimentation is not practical, even with the spinal cord held in position by a system of spinal clamps. The slightest movement of the nervous tissue under observation is inimical to the successful recording of "spike-like" activity with rigid microelectrodes. To describe further the functional state of these preparations, it may be noted that they usually exhibited a strong tonic motoneuron discharge (Fig. 12A), which in the absence of vestibular background was probably maintained by the constant influx of afferent impulses from the periphery (Barron and Matthews, 1935). A record of this tonic afferent activity will be presented in another connection (Lloyd, to be published). It is probable, in the light of recent studies (Marshall, Woolsey, and Bard, 1941; Lloyd, 1941a) that the low concentration of barbiturate present in these preparations (some were observed as long as 14 hours after the administration of nembutal in amounts sufficient for initial basal narcosis) did not interfere appreciably with primary responses to pyramidal stimulation.

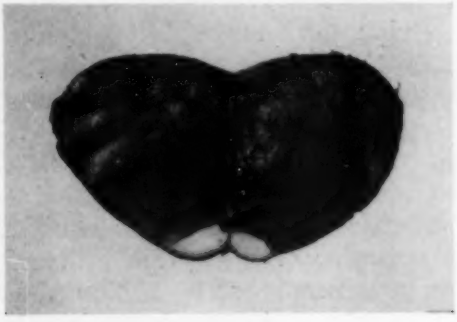

FIG. 1. Gross specimen to illustrate the standard lesion placed at the level of the inferior olives by means of a spring guillotine. The medulla was removed at the end of the experiment and fixed. After fixation the specimen was rapidly surface-stained, washed and blotted. The lesion was completed and the cut face of the transected medulla photographed. The unstained area shows the extent of the cross-sectional area that is spared by the guillotine, and hence the maximum conducting tissue between the stimulating electrodes and the spinal cord.

Stimulating electrodes were placed through the floor of the fourth ventricle until the bared tips embraced the pyramid at the level of the trapezoid body. Cranially a complete transection was placed at the collicular level. The lesion caudal to the electrodes was accomplished by means of a spring guillotine. As the blade of this guillotine passes ventrally through the medulla until the curved free border reaches the basiocciput, a central notch in the blade permits the pyramids and basilar artery to escape damage. Figure 1 illustrates, in a macroscopic preparation, the extent of the standard lesion produced by the guillotine at the level of the inferior olives. The medulla was removed from each preparation at the end of the experiment, and the lesion inspected after fixation.

Records were obtained by means of fine steel wire microelectrodes insulated but for the tip. These could be placed at will in the spinal cord with the aid of a micromanipulator, used with due regard for deformation error. Approach to regions of the gray substance from various angles in many experiments has diminished the hazard inherent in mechanical error. The highest degree of accuracy cannot be claimed in the absence of histological control;

however, the latitude in localization which has been allowed for in the responses to be described is ample to compensate for the errors involved.

Conduction in the pyramidal tract. A single shock to the pyramid results in a volley of impulses which is conducted caudally throughout the length of the spinal cord. The response of the pyramidal fibers may be recorded from a highly localized area equal to approximately 1 sq. mm. of the cross-sectional area of the cord, and situated as expected in the cat, in the lateral column adjacent to the dorsal horn (cf. Spitzka, 1886; Lenhossék, 1889; Bechterew, 1890). Figure 2 illustrates the pyramidal tract response to single shocks recorded at various conduction distances. One would expect the pyramidal fibers conducting impulses past the recording microelectrode to yield impulses recordable as triphasic spike potentials (for a recent discussion cf. Lorente de Nó, 1939, p. 430 *et seq.*). An attempt to obtain such records even at short conduction distances has been only partially successful. For example, Fig. 2A shows a small negative deflection recorded at a conduction distance of 6.8 cm. If the recording microelectrode is thrust boldly into the region occupied by the pyramidal fibers, or having passed through that region is brought back along its own track, a large, predominantly positive potential results. Figure 2B which shows such a positive potential, was recorded from the same point as was Fig. 2A. Similar effects have been noted by Therman (1941) when attempting to record from the medial lemniscus, and by Bishop and O'Leary (1941) in the superior colliculus. The origin of the predominantly positive responses, such as are shown in Fig. 2, is not entirely clear. Part at least of the initial positive deflection may be ascribed to the impulses approaching from a distance. Consequently it is difficult to designate exactly the time of arrival of impulses at the recording electrode from such records. Damage is an undoubted factor, but some of the recorded impulses reach or pass the electrode, for there are spike potentials in the records having a prominent negative phase, although they are submerged by positivity. The resultant records probably indicate a dispersed discharge

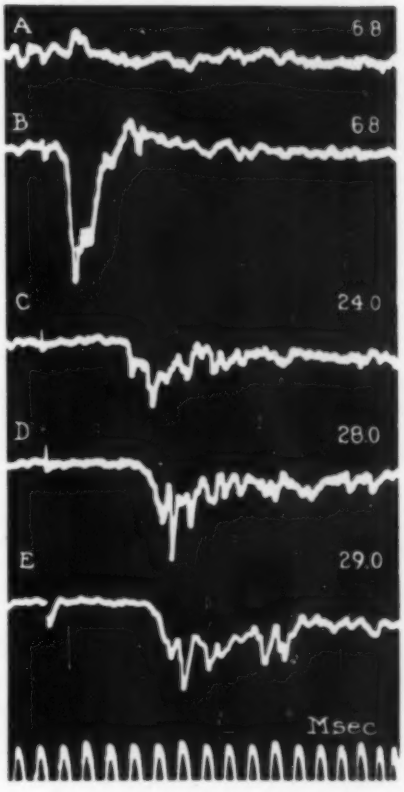

FIG. 2. Activity instituted by single pyramidal volleys and recorded by microelectrode from the pyramidal tract at the conduction distances designated in centimeters at the right. A to D from one preparation. E from another preparation for comparison. Time in msec. Further description in text.

in a number of elements, some of which are blocked at a short distance from the electrode, some of which are blocked at the electrode, and some of which are unblocked.

Records 2C, D, and E were obtained in the same way as was 2B, but at the designated conduction distances. Records 2A to D were obtained from a single preparation. Record 2E is from another preparation for the purpose of comparison. A slope of the latencies in 2B to D reveals a conduction rate of approximately 63.5 M per sec. for the most rapidly conducting fibers of the tract. This value was approximated in all the experiments of this series.

Determination of the lower limit of pyramidal fiber velocities is fraught with uncertainty. The activity as recorded from the tract has no clearly defined termination. The tract itself has intimate anatomical relationship with cellular elements which are known to discharge in response to the tract impulses (cf. next section). Thus, although the pyramidal response certainly suffers considerable temporal dispersion, no definitive value may be given for the lower limit of velocities. A study of the records suggests that an estimate of 18 M per sec. is not too low for the lower limit of velocities, although in view of the large numbers of very fine fibers to be found in the pyramidal tract of the cat (McKibben, and Wheelis, 1932; Lassek and Rasmussen, 1940), this value may be far too high.

The activity illustrated in Fig. 2 is the only tract activity that has been recorded from the white columns of the spinal cord following pyramidal stimulation, as would be expected from a consideration of the anatomical studies of Lenhossék (1889) and Bechterew (1890) on the cat's spinal cord.

It is important to recognize the implications of the fact that the pyramidal tract, subsequent to synchronous activation at the level of the medulla, delivers into the lumbar enlargement, by virtue of dispersion, a prolonged asynchronous discharge. In consequence some features of the tract activity will resemble those of a diffuse nuclear discharge. The major principle is: that time lost by slow conduction is in some measure the formal equivalent of time lost in the synaptic relaying of otherwise rapidly conducting pathways. For example, it will be seen that the most rapidly conducted impulses evoked by a second pyramidal shock will be capable of summation with the more slowly conducted impulses evoked by an antecedent similar shock, given an interval of several milliseconds between shocks and a similar distribution of terminal knobs.

Responses of the Gray Substance

(1) *The external basilar region (Cajal).* Following a single shock to the pyramid, and the consequent arrival of a dispersed volley of pyramidal impulses in the lumbar enlargement, certain interneurons within the cord become active. The resulting activity is discernible often only as a slow potential change of some 40 to 45 msec. duration. Under favorable conditions however, a burst of small spike potentials occupying the period of the slow potential wave is recorded. An experiment of this kind is presented in Fig. 3. Record 3A shows the level of noise and activity maintained in the absence

of any specific stimulation. The recording tip of the microelectrode was placed in the extreme lateral margin of the base of the dorsal horn (external basilar region, Cajal, 1909). The anatomical position is confirmed by the appearance in the record (3B) obtained with a single pyramidal volley, of both pyramidal impulses (p) and nuclear discharges (e). The pyramidal impulses recorded in Fig. 3 are probably occupying pyramidal collaterals to the gray substance. The pyramidal impulses begin after a latency of approximately 4 msec., are again of positive sign (indicating damaged bundles of fibers), and are accompanied almost immediately by a flame of small spike potentials, the latter making up a discharge not greater than 50μV. in amplitude with a duration of some 40 msec. It seems certain, by reason of the fine and obviously non-unitary character of the nuclear discharge, that it may be assigned to a dense population of small elements situated at the lateral aspect of the base of the dorsal horn, and intermingled with fascicles of pyramidal collaterals.

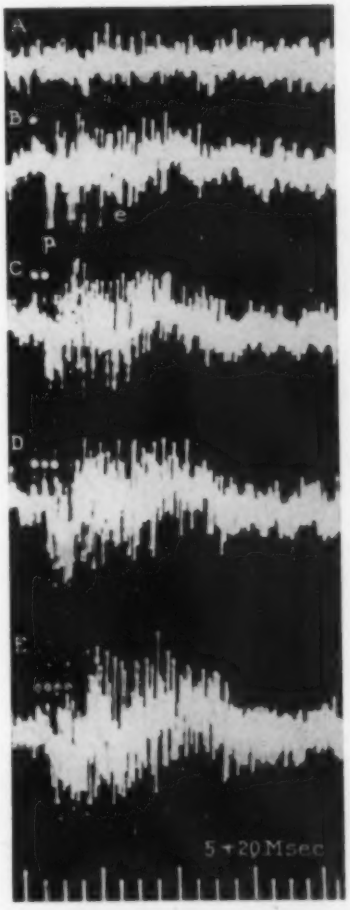

FIG. 3. Activity recorded at the extreme lateral aspect of the base of the dorsal horn. The stimulation artifacts of the pyramidal shocks are marked by dots. Pyramidal impulses and nuclear discharges are identified in B (p and e respectively). Time, in 5 and 20 msec. intervals, is shown at the bottom. In all figures where there are two time designations, these are for the small and large divisions respectively. Further description in text.

The close functional relationship between the pyramidal tract and nuclear elements at the base of the dorsal horn forces the opinion that the pyramidal fibers impinge, either terminally or collaterally, upon these elements. This interpretation agrees best with the view held by Schäfer (1899), who stated that the pyramidal fibers enter the gray substance at the base of the dorsal horn and end in relation to cells of that region. Other zones of termination are not excluded; for instance, although the type of discharge at present under consideration appears to be more prominent at the external basilar region of Cajal, it is probable that small elements reacting to pyramidal stimulation in a similar manner are more widespread. A suggestion of low amplitude discharges is to be found in other regions following single shocks to the pyramids (Fig. 5B, 6A and G). It is difficult to affirm that these discharges in other regions result clearly, from the pyramidal stimulation. Hence it would be gratuitous to assume, on this basis alone, a more widespread distribution of pyramidal fibers, although

some histological studies on the cat do point to this direction (Hoff, 1932).

Records 3C, D, and E show the manner in which the fine basilar discharge is intensified by the addition of successively greater numbers of pyramidal shocks. It is only after a degree of intensification approximating that seen in Fig. 3D and E, that other types of activity have been found in other regions of the gray substance, *i.e.* intensification of activity in one region is accompanied or followed by spread of activity to other regions. The active regions, subsequent to spread, include the solitary cell region of the dorsal horn and the intermediate region.

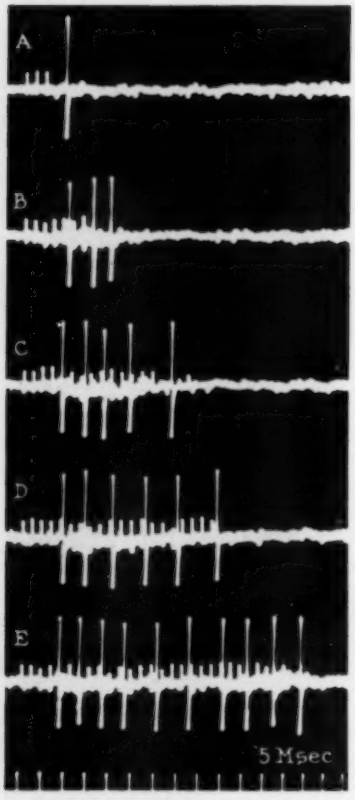

FIG. 4. Activity found in the center and base of the dorsal horn. The small regular deflections are the recorded stimulus artifacts of the pyramidal shocks. The large spike potentials (about 2 mV.) constitute the solitary cell response to pyramidal stimulation.

(2) *Solitary cells (Lenhossék) of the dorsal horn.* The responses obtained in this region have all the characteristics that would be expected from a group of large cells sparsely scattered through a "matrix" of smaller elements. The correlation between functional picture and histological description (Lenhossék, 1895; Cajal, 1909; Bok, 1928, etc.) appears to justify the argument that the discharges under consideration are recorded from the solitary cells of the dorsal horn. The responses are localized, and when found, are relatively uniform in amplitude and fairly regular in frequency when subjected to a prolonged pyramidal tetanus (Fig. 4). At no time in this series of experiments have two similar units of the solitary cell type been detected at the same microelectrode position. On the basis of general experience this fact would indicate that the units are few in number and widely spaced. In general, all the criteria upon which the assumption of unitary response is customarily based (cf. Adrian and Bronk, 1928, etc.) are satisfied. The amplitude of the spike potentials recorded from these units is large, being usually of the order of 2mV. It may be stated parenthetically that the only larger spike potentials (up to 6mV) which have been encountered in the spinal gray substance so far are those attributable to motoneurons.

Figure 4 illustrates the characteristic discharge of a solitary cell unit of the dorsal horn when driven by pyramidal tetani of increasing durations. As seen in Fig. 4A, three pyramidal shocks are necessary to produce the first and single response of the unit. As the tetanus is lengthened (4B to 4E) subsequent discharges occur. A glance at the records of Fig. 4 suffices to show that

there is a roughly direct relationship between the duration of the pyramidal tetanus and the number of discharges obtained from this unit. Even so the discharge frequency bears no direct and exact relationship to the stimulus frequency.

The solitary cell discharge takes place on a background of small cell activity that may be identified in the observations of Fig. 4. It is probable that the highly asynchronous activity of the small units in this region, as well as in the external basilar region, constitutes a slowly changing, statistically smooth over-all excitation to the large solitary cell units, and that these latter in turn respond at intervals determined in part by their own properties (cf. Lorente de Nó, 1938, p. 226). The facts, (i) that the solitary cell units discharge only after a 9 or 10 msec. total latent period, (ii) that summation of influences from several pyramidal shocks is necessary to procure a discharge, and (iii) that the stimulus frequency is not evident in the response (cf. with Fig. 7) suggest that the internuncial contribution to the solitary cells is of relatively greater importance than is that of the pyramidal fibers themselves. It is not possible to exclude pyramidal fibers from synaptic relationship with the solitary cells. Whether or not the solitary cells represent important relays distributing pyramidal activity of the motoneurons of the same side depends naturally upon the distribution of the solitary cell axons. Some of these cells have axons passing through the ventral commissure to the opposite side, some have uncrossed axons reaching to the lateral columns (Cajal, 1909; Bok, 1928). The latter might be regarded as reaching the motoneurons of the same side. It is furthermore possible, on the basis of time relationships, that the solitary cells relay activity to the intermediate region.

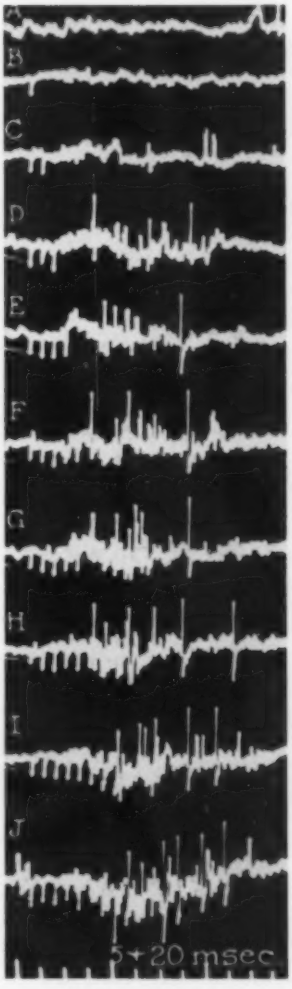

FIG. 5. Activity in the intermediate region resulting from one (B) to nine (J) pyramidal shocks. The level of "resting" activity is shown in A. Further details in text.

(3) *The intermediate region, including the intermediate gray nucleus of Cajal.* Units throughout the intermediate region discharge impulses in response to a short train of shocks to the pyramid. The spike potentials yielded by these units have an amplitude of 200μV. to 1 mV, in general, intermediate in amplitude between the spike potentials of the two groups already considered. The individual units of the intermediate region are not as discrete as are the solitary cells, as evidenced by the fact that

even the most favorable records usually contain spike potentials from several similar elements. The intermediate response is most prominent in the ventral part of the intermediate region.

The latent period for activity of the intermediate type varies usually between 12 and 20 msec. in duration. The method of direct recording from a few units is not the most satisfactory method for observing the average discharge latency of a neuron pool, since quite wide variations often occur between successive observations. The values given are thus of necessity estimates based upon a large number of observations in a number of experiments. The frequency of pyramidal stimulation is a factor influencing the latency of response in the intermediate region, as elsewhere. Various examples to illustrate the latency for discharge in the intermediate region may be found in Fig. 5 and 6.

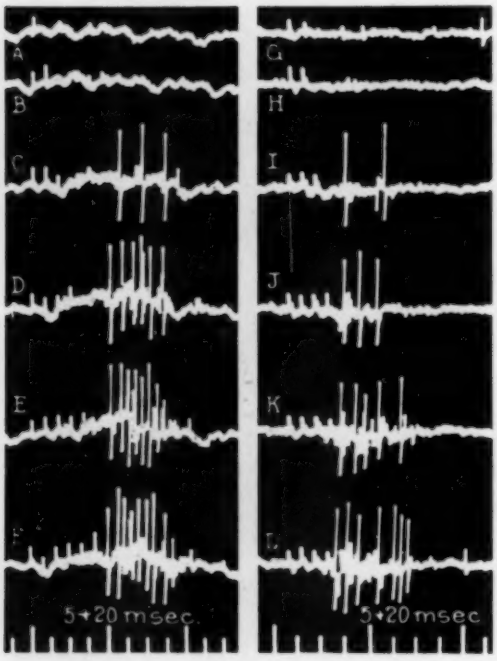

FIG. 6. Activity in the intermediate region resulting from one to six pyramidal shocks. A–F recorded from the lumbar cord. G–L recorded from the cervical cord. Note the difference in total latency for activation of the intermediate regions of cervical and lumbar enlargements under otherwise similar conditions, also background discharges of low amplitude.

Figure 5 demonstrates the effect of applying successively longer trains of pyramidal shocks upon the activity in the intermediate region. The microelectrode in this experiment was placed 2.0 mm. below the dorsal surface of the cord, just medial to the root entry line. A comparison of record 5A, in which no stimulus was given, with 5B, in which a single pyramidal shock was delivered, indicates clearly that a single pyramidal volley does not precipitate activity of the intermediate type. It is only in record 5D, obtained with the use of three pyramidal shocks, and in the subsequent records of Fig. 5, that unmistakable activity of intermediate type is to be found. The fact that several pyramidal shocks are necessary to bring about the intermediate type activity has been regularly and repeatedly confirmed. Other examples of this observation may be found in Fig. 6A to F, recorded again from the lumbar enlargement, and in Fig. 6G to L, recorded from a similar region in the cervical enlargement. It is of particular interest that several pyramidal volleys are required to obtain an intermediate type discharge in the cervical cord, for there dispersion of the pyramidal tract volleys is so much less (compare Fig. 2B with Fig. 2C, D,

and E). It may be inferred that dispersion of the pyramidal impulses *per se* is not the primary cause of the failure of the intermediate region to respond to single pyramidal volleys.

A comparison of the activity characteristic of the intermediate region with that most prominent at the external basilar region (Fig. 3) shows that the former only occurs under conditions which are known to intensify the latter, and furthermore, that the former begins later and ends earlier than the latter under similar durations of pyramidal stimulation. A study of Fig. 5 and 6 reveals that the intermediate type activity appears on a background of fine discharges which are in no fundamental sense different from those in the external basilar region. The relationship between small cell activity (external basilar and intermediate) and the intermediate type activity is such as to lead to the conclusion that the intermediate type units become active largely as the result of discharges projected from the small cell elements. This conclusion does not exclude the possibility of direct synaptic connections from pyramidal fibers. Connections of the latter sort must in fact be considered for the following reason (cf. Fig. 7).

FIG. 7. Example of nuclear elements of the intermediate region following exactly the pyramidal stimulus frequency. As the frequency is high, a fairly close relationship between between tract fibers and these nuclear elements is indicated.

In the responses presented so far there has been no indication that units of the gray substance follow the frequency of the pyramidal stimulus. This may not be cause for surprise, since dispersion is great and the stimulation frequency high (cf. Bronk, Pitts, and Larrabee, 1940). Figure 7, however, shows a single experiment in which a unit was found to follow exactly the stimulation frequency. The micro-electrode was placed in the intermediate region (2.1 mm. down, 0.5 mm. medial to the root entry line). In each record of Fig. 7 (all similar) some of the responses are dropped. The dropped responses are the fifth, seventh, and eighth in A; the fourth and seventh in B; and the sixth and eighth in C. Discounting the dropped responses, the remainder are absolutely fixed with respect to the causal pyramidal shocks. The facts (i) that shortening of the pyramidal pathway to this unit does not take place (cf. discussion in connection with Fig. 11), and (ii) that some elements of the intermediate gray substance can be driven at the (high) frequency of the pyramidal volleys indicate a rather close anatomical connection between pyramidal fibers and such intermediate elements.

Facilitation of motoneurons by pyramidal action. The two-neuron-arc re-

flex discharge described by Renshaw (1940) has proved of value for the purpose of testing the average excitability of a segmental population of motoneurons. Since the motoneuron discharge that results from short trains of pyramidal shocks cannot be measured with any degree of accuracy, it has been necessary to rely upon alterations in testing two-neuron-arc reflex discharges for a reliable gauge of pyramidal influence over the motoneurons.

Figure 8 shows plotted curves constructed from an experiment in which the influence, on the two-neuron-arc discharge, of one to six pyramidal shocks was examined. The coordinates show the amplitude of the two-neuron-arc discharge as a function of time after the onset of the pyramidal stimulation. A single or two pyramidal shocks (curves 1 and 2) had no effect on the motoneurons that could be detected by the method. Three shocks resulted in a brief period of facilitation in the motor pool, after a total latent period of approximately 12 msec. The total latent period for facilitation at the motoneuron level varies from 12 to 20 or more msec., its duration being, in part, a function of the frequency of pyramidal stimulation (compare the motoneuron facilitation curves of Fig. 9A and B). Figures 9, 10, and 11 show examples from other experiments of the total latency for motoneuron facilitation. The values found in these experiments were approximately 14 and 18, 15.5, and 12 msec. respectively.

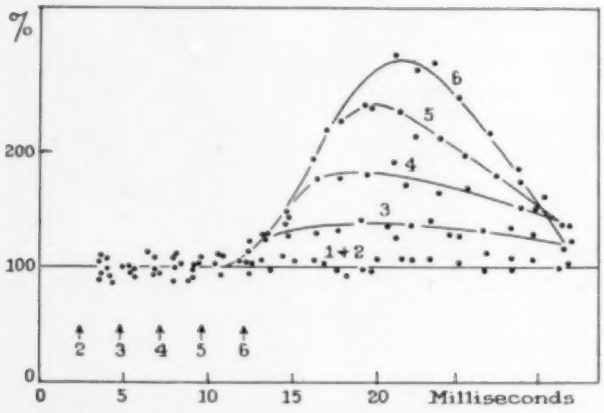

FIG. 8. Facilitation of spinal motoneurons by pyramidal activity. Amplitude of the two-neuron reflex response (ordinates) is plotted against the interval at which the reflex follows the single pyramidal shock, or first pyramidal shock of a train. The numbered arrows indicate the timing of the pyramidal shocks. The number of each curve of the family identifies that curve with the number of pyramidal shocks employed in the conditioning stimulation. Amplitude of the test response in isolation is 100.

As more pyramidal shocks are added to the train, facilitation of the motoneurons increases in intensity (Fig. 8, curves 4, 5, and 6). The duration of the facilitation period due specifically to the sixth pyramidal shock (obtained by subtracting the area enclosed by curve 5 from that enclosed by curve 6) is much shorter than is the duration of the facilitation period specifically related to the third shock (area enclosed by curve 3). Thus, to parallel the increase in intensity there is a more rapid summation of subnormality (Gasser, 1935; Lorente de Nó and Graham, 1938) that occurs at the pre-motoneuron level rather than at the motoneuron level itself, for the feeble motoneuron discharge is not likely to evoke significant motoneuron subnormality. On

this interpretation, the more rapid failure of pre-motoneuron activity consequent upon more intense activation would increase reflex threshold in the ventral horn secondarily by diminished opportunity for summation there.

A comparison of facilitation in the motor nucleus (Fig. 8, also Fig. 9, 10, and 11) with discharges recorded from the intermediate region of the gray substance (Fig. 5 and 6) shows that the two events are closely parallel. Given anatomical connection (Kölliker, 1890; Cajal, 1909; and others), the parallelism appears to establish a causal relationship. The conclusion may be reached that activity in the intermediate region, following pyramidal stimulation, is the principal contributing factor to excitation in the motoneuron pool. The solitary cells of the dorsal horn, as stated above, may form additional links between the pyramidal fibers and the motoneurons.

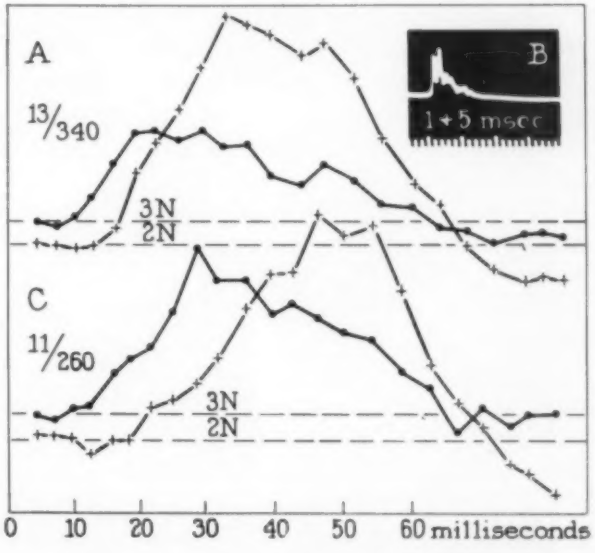

FIG. 9. Facilitation of two-neuron and three-neuron reflex arcs by pyramidal activity. Inset B shows the reflex discharge in response to the test dorsal root volley. The first two spike potentials of B represent activity through arcs of two and three neurons respectively. The amplitudes of the two-neuron response (crosses) and three-neuron response (circles) are plotted in A and C as functions of time after the first shock in a train of pyramidal shocks. The hatched lines, 3N and 2N, of A and C show the amplitude of the test responses in isolation. In A, 13 shocks at 340 per sec. provided the conditioning activity. In C, 11 shocks at 260 per sec. were used for conditioning. Full description in text.

Facilitation of reflex arcs at internuncial levels. Just as the two-neuron-arc discharges have proved of use for testing the excitability of motoneurons three-neuron-arc reflex discharges now prove to be equally useful in detecting average excitability changes at the internuncial level, when evaluated in terms of alterations in discharges mediated through arcs of two neurons. In theory, three-neuron-arc reflex discharges may be facilitated at two points; at the junction of primary afferent neurons with interneurons, and at the junction of interneurons with motoneurons. If, however, a three-neuron-arc discharge be facilitated in the absence of any change in the concomitant two-neuron-arc discharge, it may be said that the facilitation has occurred at the internuncial level.

Figure 9 illustrates the effect of pyramidal stimulation on reflex discharges pertaining to arcs of two and three neurons. The inset B of Figure 9 shows the dorsal to ventral root reflex discharge resulting from a single

shock. The first two clearly defined spike potentials, separated in time by approximately 0.7 to 0.8 msec., are the two and three-neuron-arc discharge spike potentials respectively. It is the amplitudes of these two spike potentials that are plotted in Fig. 9A and C, as a function of time after the onset of the pyramidal stimulation. In Fig. 9A, 13 shocks were delivered to the pyramid at a frequency of 340 per sec.

Facilitation of the two-neuron-arc response in Fig. 9A (crosses) begins approximately 14 msec. after the onset of the pyramidal stimulation. In contrast, facilitation of the three-neuron-arc reflex discharge (circles) begins several milliseconds earlier, at about 9 msec. after the first pyramidal shock. Thus for a period of approximately 5 msec. the three-neuron-arc may be regarded as being facilitated only at the internuncial (pre-motoneuron) level. A time differential amounting to as little as 3 msec. between the facilitation of three-neuron and two-neuron-arc discharges has been encountered. The total latency for facilitation of three-neuron-arc discharges varies between 9 and 12 msec. Because the beginning of the solitary cell discharge (Fig. 4) falls within the 9 to 12 msec. time range, it is possible that the solitary cells supply impulses by collaterals to the interneurons occupied by the three-neuron-arc discharges.

As the facilitation of two-neuron-arc discharges progresses, there is a secondary decrease in the amplitude of the facilitated three-neuron-arc discharge, which undoubtedly indicates that a strongly facilitated two-neuron-arc discharge occupies more of the motoneurons that would otherwise be at the service of three-neuron arcs, *i.e.* the facilitated two-neuron-arc discharge occludes the succeeding three-neuron-arc discharge (the law of plurality of connections, Lorente de Nó, 1933, 1938).

The view that two and three-neuron-arc discharges have some degree of reciprocal relationship is strengthened by a consideration of the curves presented in Fig. 9C. Figure 9C is similar to Fig. 9A, with the single exception that 11 shocks were delivered to the pyramid at a frequency of 260 per sec. With the slower frequency of stimulation employed in Fig. 9C, motoneuron facilitation (crosses) begins later (about 18 msec. after the first pyramidal shock) and progresses more slowly to reach a later maximum. Facilitation at the internuncial level also begins later and progresses more slowly. However, the added delay in facilitation is greater at the motoneuron level than at the internuncial level, with the result that the three-neuron-arc discharge may develop further before measurable occlusion begins by virtue of facilitated two-neuron-arc discharges.

In some experiments the two-neuron-arc discharge is so completely dominant in the unisegmental reflex that it becomes impossible to analyze events in higher order chains. Conversely, if a bisegmental reflex is substituted for the unisegmental reflex as a test system, an opportunity arises to study the behavior of three-neuron arcs relatively unencumbered by strong two-neuron-arc discharges. Figure 10 presents records from an experiment in which the bisegmental reflex discharge (10B) is conditioned at various time intervals

by 6 pyramidal shocks (10A). The earliest two-neuron-arc discharge occurs in 10H. Between H and O of Fig. 10, two-neuron arcs are facilitated, and presumably less direct reflex pathways also can be facilitated at the motoneuron level. Observations D, E, and F show that delayed segments of the reflex discharge are facilitated before the onset of facilitation at the motoneuron level. In 10G, the three-neuron-arc spike potential (still the initial spike potential of the reflex) is just overlapping the beginning of the period

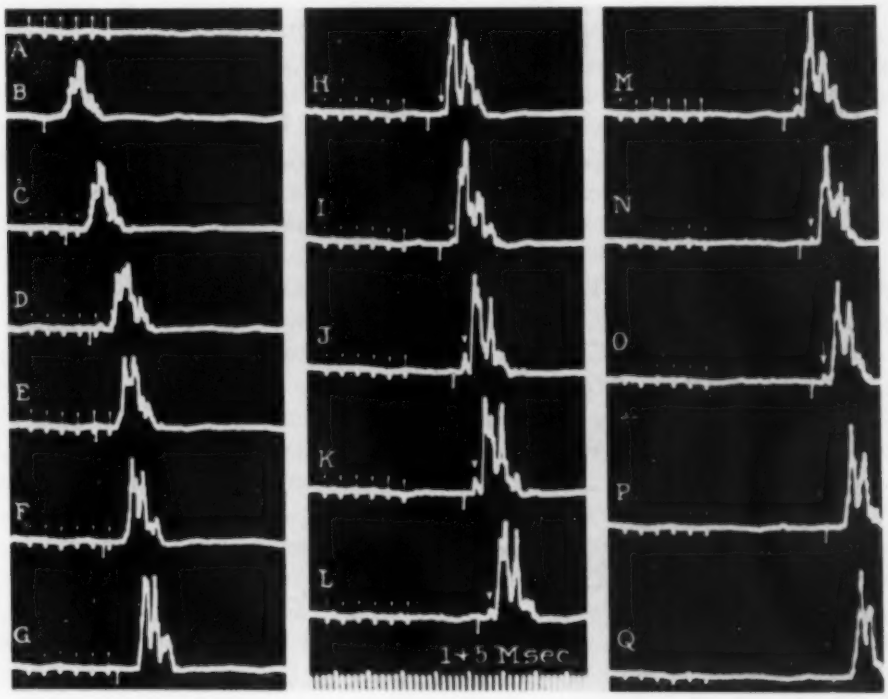

FIG. 10. Effect of six pyramidal shocks on bisegmental reflex discharge (L7–S1). Recording leads on S1 ventral root. A, response to six pyramidal shocks. B, response to testing L7 dorsal root shock. In C to Q, the test dorsal root shock falls progressively later with respect to the pyramidal train. Two-neuron-arc discharges are identified by arrows.

during which facilitation is known to occur at the motoneuron level. The two-neuron-arc facilitation is maximal in 10J, but even so it is so small that it does not interfere measurably with facilitation of the three-neuron-arc discharge. Occlusion, which is a prominent feature in Fig. 9, is not detectable in Fig. 10, in which the two-neuron-arc discharge is small. This fact again points to the multiplicity of connections between primary afferent collaterals and spinal motoneurons.

In Fig. 10 P and Q are of interest because they show, in the absence of occlusion at the motoneuron, that higher order reflex discharges (conspicuously the three-neuron-arc discharge) are strongly facilitated after facilitation in the two-neuron-arc is no longer in evidence. The period during which

facilitation at the internuncial level of the three-neuron-arc, including certainly the intermediate gray nucleus of Cajal, may be demonstrated, by the use of bisegmental testing reflex discharges, parallels the discharge period of the external basilar region. Undoubtedly the two events are related. Furthermore, Fig. 10 shows that the internuncial level of the three-neuron-arc receives facilitating impulses for a longer period of time than it discharges impulses in turn to the motoneuron pool. Thus the evidence of Fig. 10 agrees closely with that of Fig. 8, employing similar conditions of stimulation in another preparation, and again points to the intermediate region (internuncial level of the three-neuron-arc) as the locus at which failure of the spinal mechanism to transmit pyramidal excitatory action first occurs.

The time interval between the onset of facilitation of the three-neuron arcs and of the two-neurons arcs is a measure of the time between the beginning of impulse arrival in the intermediate gray nucleus, and the beginning of impulse arrival in the motoneuron pool. Since the discharge of impulses in the intermediate region coincides with the arrival of impulses in the motoneuron pool, and since the two groups of neurons are synaptically related, the time difference between facilitation of three and two-neuron-arc discharges (Fig. 9 and 10) may be taken as a measure of the "nuclear delay"* in the intermediate nucleus.

Since the total latency for excitation at the motoneuron level is so long, it becomes of interest to determine if possible the shortest functional pathway that may be established by later volleys in a pyramidal tetanus, working on the background of activity supplied by antecedent volleys. An estimate may be reached by measuring the latency from a specific shock in the train of shocks to the onset in the motor nucleus of an effect attributable to that shock. For example, the onset of facilitation in Fig. 8, after 12 msec. total latency, is in part the result of the application of the third pyramidal shock 4.8 msec. after the initial shock of the series (Fig. 8, curve 3). This is the case since the first two pyramidal shocks had no tangible effect on the motoneurons (Fig. 8, curves 1 and 2). The resulting specific latency for the third shock amounts to approximately 7.2 msec. An accurate estimate of the specific latencies for the fourth, fifth, and sixth shocks in the experiment illustrated in Fig. 8 is not possible. Figure 11, therefore, presents curves from another experiment, which embody many more individual observations. As in Fig. 8, two pyramidal shocks had no measurable effect on the motor pool. The third shock of the train produced, by intensification and spread, a period

* Nuclear delay may be defined as the observed discrepancy in time between the arrival of impulses in a nucleus and the discharge of impulses from that nucleus. Thus it might be the equivalent of the recruitment period or even of a utilization period; it could not be the equivalent of synaptic delay (cf. Lorente de Nó, 1935). Nuclear delay is a function of the presynaptic elements of the nucleus because, when the intermediate nucleus is activated (i) through the pyramidal system, nuclear delay amounts to 3 or more msec.; but when activated (ii) through primary afferent collaterals, nuclear delay can occupy no more than a fraction of a msec. A unique and definitive account of the significance of nuclear delay as determined above is not apparent from the determinations themselves.

of facilitation in the motor pool beginning at A. The horizontal displacement of arrow 3-A denotes the specific latency between the third shock and its effect in the motor pool (approximately 7.3 msec.). On the graph are shown the facilitation curves resulting from 5 pyramidal shocks (circles) and from 6 pyramidal shocks (crosses). Since the two curves are superimposed, the point of divergence indicates the time at which the effect of the sixth pyramidal shock is first exerted on the motoneurons. Had the sixth shock maintained the same specific latency as that of the third, the facilitation curves of Fig. 11 would diverge at B, since the horizontal displacement of arrow 6-B was drawn to equal that of arrow 3-A. Such is obviously not the case. The specific latency for the sixth shock is approximately 1.5 to 2 msec. shorter, *i.e.* 5.3 to 5.8 msec. in duration. Of this specific latency 4 to 4.5 msec. is attributable to pyramidal tract conduction, assuming the more rapidly conducting tract fibers to be involved. The remainder (0.8 to 1.8 msec.) is lost in the spinal mechanism, and it is of such time dimension as to suggest indirect pyramidal action on the motoneurons through internuncial relays. Since the present argument is based largely on time relationships, it will be seen that it is not necessary to assume the intercalation of interneurons between the more slowly conducting pyramidal fibers and the motoneurons. The action on motoneurons of direct pyramidal connections, if they exist, must be small, for it has not been detected by the use of single pyramidal volleys.

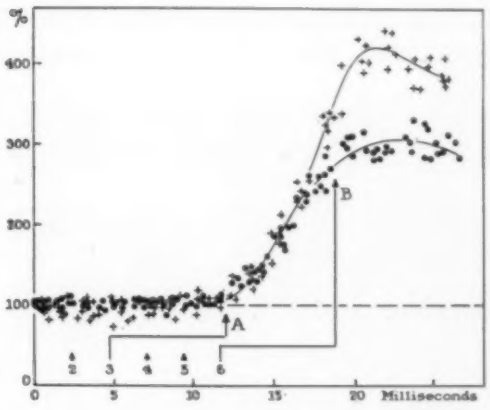

FIG. 11. Facilitation of motoneurons by 5 pyramidal shocks (circles) and 6 pyramidal shocks (crosses). The curves are constructed as in Fig. 8, the two-neuron-arc discharge again being used as a test. The arrows numbered successively at the bottom indicate the timing of the pyramidal shocks. The interval between the time of the sixth shock and the point of divergence of the two facilitation curves denotes the specific latency between the sixth shock and its effect in the motor pool. Arrow 3-A denotes the specific latency for the third pyramidal shock. Arrow 6-B has the same time span as Arrow 3-A. Note that the curves diverge before B; hence there is progressive shortening of latency in the spinal mechanism.

The discharge of motoneurons in response to pyramidal stimulation. In many of the experiments of the present series a regular tonic discharge of impulses from the motoneurons has been detected readily by means of recording leads placed on a ventral root (Fig. 12A). Tonic innervation is well-known in the decerebrated preparation (decerebrate rigidity—Sherrington 1897; cf. Denny-Brown, 1929; Adrian and Bronk, 1929). However, the tonic discharge of spinal motoneurons under the conditions of the present experi-

ments is not a manifestation of decerebrate rigidity, for the vestibular and reticular pathways are severed (cf. Fulton, Liddell, and Rioch, 1930a, b), nor can it be due to maintained discharges from the cerebral cortex (Adrian and Moruzzi, 1939), because the brain stem is transected routinely at the colliculi. There remains the continuous flow of afferent impulses entering through the dorsal roots, previously mentioned. The tonic afferent discharge is probably the major factor in maintaining the tonic motoneuron discharge in the spinal animal. The tonic motoneuron discharge seen in these preparations is probably related to the flexor rigidity of Dusser de Barenne and Koskoff (1932, 1934). It may be noted that the spinal clamps that have been used in these experiments hold the preparation in a position appropriate for the development of flexor rigidity.

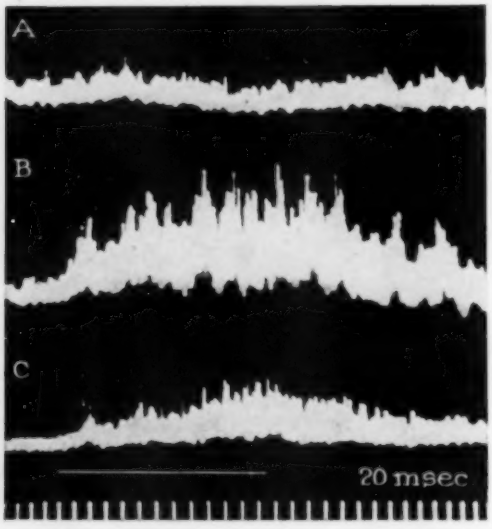

FIG. 12. Records from ventral root. A, tonic discharge of motoneurons (spinal preparation). B, motoneuron discharge resulting from pyramidal stimulation of 245 msec. duration. C, and B, but after prevention of movement by curare. Note afterdischarge in B and C. The horizontal line below C indicates the duration of the pyramidal stimulation in B and C. Further details in text.

A prolonged* pyramidal tetanus (245 msec. duration) evokes after 20 to 30 msec. latency a discharge of motoneurons which takes the form of an increase in the level of the pre-existing tonic discharge (Fig. 12B). The added discharge often shows a maximum at 35 to 50 msec., following which is a depression and a secondary increase. After the cessation of the pyramidal stimulation, the duration of which is indicated by the horizontal line immediately below record 12C, the motoneurons "afterdischarge" for several hundred milliseconds.

It is difficult to estimate the part played by the pyramidal system *per se* in these prolonged phenomena, for once movement begins, locally engendered activity, reflecting from the periphery, may supervene to reinforce the pyramidally evoked activity. For instance, after record 12B was taken curare was administered to the preparation until movement was no longer observed. Figure 12C illustrates the discharge of motoneurons obtained by the pyramidal tetanus in the paralyzed preparation. The tonic activity is less, as is the activity evoked by the pyramidal stimulation. Note, however, that the

* These stimulations are not prolonged in the sense usually accepted in studies on the pyramidal system, nor are the frequencies employed throughout comparable with those usually employed. The reason for this of course is the purpose underlying the experiments, which likewise is different.

motoneurons still maintain an afterdischarge for several hundred msec. in the curarized preparation. A comparison of Fig. 12B and C demonstrates in an elementary way the reinforcing action of secondary peripherally evoked activity.

Inhibition. Inhibitory actions frequently have been attributed to the pyramidal tract. Figure 13 presents one of several instances in which activity recorded from the intermediate gray substance was suspended rather than initiated or intensified by pyramidal stimulation. Record A of Fig. 13 illustrates the activity which was recorded in the absence of specific stimulation.* Record B of Fig. 13 shows the suspension of activity brought about by a pyramidal tetanus of approximately 100 msec. duration. Other units will be brought into activity during the time that the units at present under discussion are "inhibited" (cf. Fig. 5 to 7). Granting anatomical connection between the "inhibited" units and the motoneurons, the motoneuron discharges of Fig. 12 represent the final resultant of simultaneously occurring excitatory and inhibitory actions (direct or indirect, Lloyd, 1941b). It is not possible from the present experiments to determine whether or not the operation of reciprocal innervation, herein demonstrated for interneurons, is maintained within the motor pool by specific distribution of internuncial axons. The observations of Fig. 13 throw no light on the nature of the fundamental processes involved, which is in consequence not discussed.

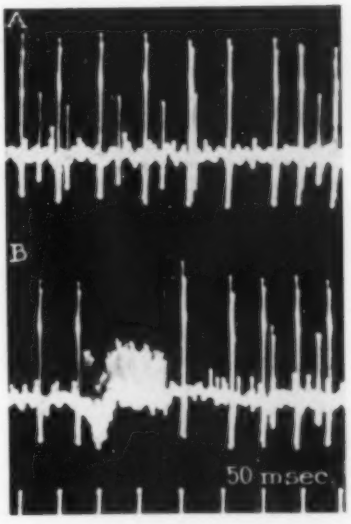

FIG. 13. Inhibition of tonic interneuron activity by pyramidal activity, (100 msec. tetanic stimulation). Note the different times at which various elements return to activity.

Functional organization of the spinal mechanism of the pyramidal tract. Figure 14 presents in diagrammatic form a summary of functional connections between fibers of the pyramidal system, primary afferent collaterals, and neurons of the spinal cord, as they appear in the light of the foregoing observations. The diagram is admittedly incomplete and imperfect. The pyramidal fibers (P) are pictured as ending most prominently on the cells of the external basilar region (E). Possible connections to the solitary cells (S) and some cells of the intermediate region are indicated. There is little indication from the present experiments that pyramidal fibers end on motoneurons (M.N.). In consequence no connections

* One is inclined to accept the physiological nature of the internuncial discharges "spontaneously" occurring in Fig. 13, for they may continue unabated for hours with amplitude and phase relationships of the spike potentials preserved. Likewise, since the preparations exhibit a constant afferent inflow and a tonic motoneuron discharge, there is no reason to suppose that the interneurons would not display activity if the recording microelectrode were not in position.

are included in Fig. 14. The cells of the external basilar region (E) relay activity to the solitary cells (S) and to the intermediate region (I and I_2). The intermediate gray nucleus of Cajal is represented (I). Primary afferent collaterals (P.A.) convey activity through branches 3 and 3a to interneurons, which in turn supply motoneurons (M.N.) thus completing three-neuron reflex arcs. Furthermore, primary afferent collaterals (P.A.) through branch 2 to the motoneurons (M.N.) complete the two-neuron reflex arcs.

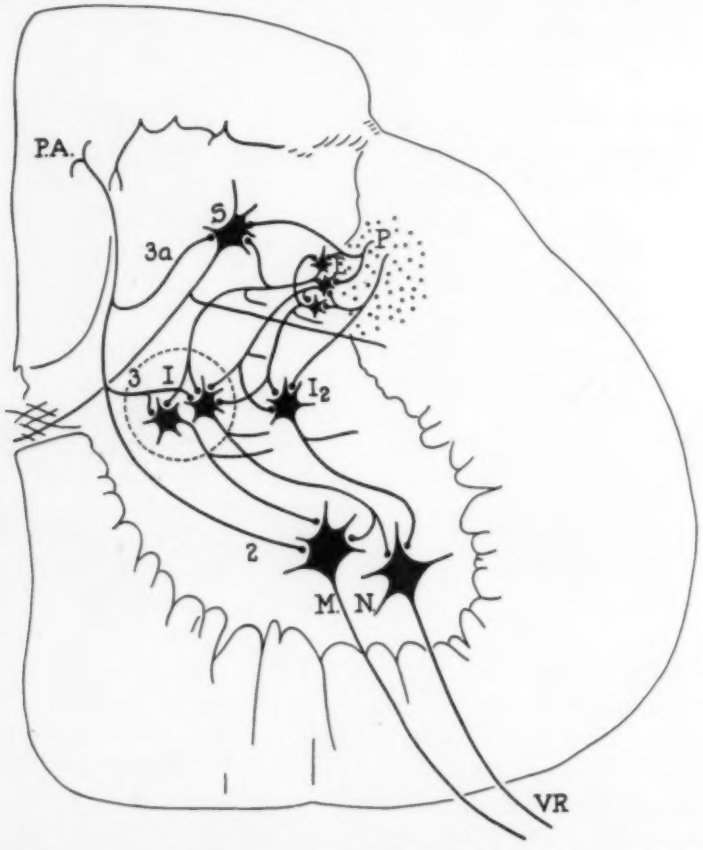

FIG. 14. Functional organization of the spinal mechanism of the pyramidal tract. Connections from the pyramidal tract and primary afferent collaterals are represented. E, small cells of the external basilar region; I, intermediate gray nucleus of Cajal; I_2, other neurons of the intermediate region; M. N., motoneurons; P, pyramidal tract and fibers; P. A., primary afferent collaterals; S, solitary cells of the dorsal horn; V. R., ventral root; 2, 3, and 3A, terminal collaterals of the primary afferent system.

Emphasis must be placed on the fact that activity within the spinal gray substance is continuous from the arrival of the first tract impulses as the result of pyramidal stimulation until the spinal mechanism reaches the highest activity level possible under the conditions of the experiment. Within the stroma of continuous activity certain neurons, or groups of neurons, become

active at well defined and reproducible time intervals after the onset of the pyramidal stimulation. The dynamic characteristics of the spinal mechanism of the pyramidal tract may be summarized by a brief recapitulation of two type experiments. In the first type experiment a single pyramidal volley is used. Pyramidal impulses first enter the lumbo-sacral cord at 4.5 msec. after the pyramidal shock and continue to do so for possibly 10 or more milliseconds (Fig. 2). They are accompanied by a burst of nuclear activity in the external basilar region (Fig. 3). Other types of internuncial activity do not ensue, nor is reflex activity affected demonstrably throughout the activity period. Presumably following a single pyramidal shock, the impulses of the external basilar region (E in Fig. 14) circulate within the nucleus itself, extranuclear discharges through longer collaterals to other nuclei being negligible. In the second type experiment several pyramidal shocks are used. The minimal latency of pyramidal conduction is 4.5 msec. as before, but tract activity and external basilar region activity are intensified by the added pyramidal shocks. The contribution of impulses to other internuncial nuclei becomes sufficiently great to result in measurable facilitation at the internuncial level of the three-neuron reflex arc at 9 msec. after the onset of the pyramidal stimulation. Thus approximately 4.5 msec. are lost in the dorsal horn. An additional 3 msec. are lost in nuclear delay at the intermediate region before intermediate neurons discharge and motoneurons are facilitated. Thus the total latent period for facilitation of motoneurons (12 msec.) is accounted for by (i), tract conduction (4.5 msec.); (ii), dorsal horn latency (4.5 msec.); and (iii), nuclear delay at the intermediate level (3 msec.)

As activity spreads slowly through the spinal gray substance, progressively shorter functional pathways are opened to the pyramidal impulses, so that the time lost in the internuncial pools of the spinal gray substance is reduced from approximately 7.5 msec. to approximately 1.0 msec. (Fig. 11).

When pyramidally evoked activity reaches the motoneurons, the motoneuron discharge realized through three-neuron reflex arcs may be facilitated at both the interneuron and motoneuron levels. If a large two-neuron-arc response is present in the test reflex discharge, occlusion of the three-neuron-arc discharge at the motoneuron level counteracts the facilitatory action of the pyramidal stimulation.

Summary

A method is described whereby a controlled pyramidal volley may be delivered into the spinal cord. Using this method, an attempt is made to outline the functional organization of the spinal mechanism under the conditions of pyramidal stimulation. A summary of this organization is presented in connection with Fig. 14. Cats were used.

Pyramidal activity is distributed along the length of the spinal cord by the pyramidal tract fibers. The most rapidly conducting of these have a velocity between 60 and 65 M per sec. The lower limit of pyramidal fiber velocities is uncertain, but dispersion of a volley, initially synchronous at

the medullary level, is sufficient to produce a discharge of pyramidal impulses into the lumbar cord lasting many milliseconds.

Interneurons of the spinal cord are of paramount importance in effecting the distribution of pyramidal activity. Small nuclear elements, in close proximity with the tract, appear to constitute the initial internuncial relays. The final or premotoneuron internuncial relays lie within the intermediate region. Facilitation of motoneurons, as tested through primary afferent volleys, parallels activity in the intermediate region. In view of known anatomical connections a causal relationship between intermediate internuncial discharges and excitation of motoneurons appears to be established.

A nuclear delay of several milliseconds exists at the intermediate nucleus under the conditions of pyramidal excitation. The same nucleus activated through primary afferent collaterals has a nuclear delay of but a fraction of a millisecond. The differences are a function of the presynaptic elements rather than of the postsynaptic elements.

As pyramidal activity is intensified, shortening of the functional paths interposed between pyramidal fibers and motoneurons occurs. The rate of shortening is related to the frequency of pyramidal stimulation.

Whereas some interneurons of the intermediate region are activated by pyramidal stimulation, others are inhibited (reciprocal innervation).

Tonic discharge of spinal motoneurons occurs in the spinal state. This discharge is probably related to the flexor rigidity of Dusser de Barenne and Koskoff. The constant arrival of impulses from the periphery must be considered as an important factor in the maintenance of the tonic discharge in the spinal preparation.

Motoneuron discharge resulting from pyramidal activity is highly asynchronous, although without doubt some motoneuron units carry the pyramidal stimulus frequency.

Spinal reflex reinforcement of pyramidal activity begins with the onset of movement, and it may be important in determining the character of motor performance arising from cortical stimulations.

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CROSSED INHIBITION OF THE FLEXOR REFLEX IN THE SPINAL MAMMAL*†

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INTRODUCTION

CURRENT theories of inhibition may be divided into two groups. The first refers the depression of irritability to immediately preceding activity of the inhibited units; the second usually invokes specific inhibitory endings. The data presented here afford instances which cannot be explained upon the former hypothesis and accord well with the latter. In a paper published in March, 1941, Lloyd (6) reached identical conclusions from a different approach. Both researches dealt with anterior horn cells. Lloyd employed cats under Dial, we, spinal monkeys free from anesthesia at the time of recording. The independence of the two lines of evidence strengthens the argument for this class of inhibition. Its occurrence in two such divergent species affords strong support for the general application of the cases considered.

The present communication is not confined, however, to the problem of the nature and locus of crossed inhibition. Since a tenable inhibitory theory of the genesis of spinal shock has recently been advanced by Van Harreveld (16), this occasion would seem pertinent for the discussion of certain differences between inhibition curves obtained within a few hours of spinal transection and those recorded weeks after that operation. In the interest of clarity, the presentation of results opens with this phase of the subject.

RESULTS

Interaction of two successive volleys to roots or nerves of opposite sides has been studied in 24 cats, 6 dogs, and 30 monkeys. Of these, 14 cats, 4 dogs, and 8 monkeys were recorded on the day the cord was severed; 10 cats, 2 dogs and 22 monkeys at intervals ranging from 3 to 64 days after transection. Cord potentials were recorded from leads on the surface of the cord close to the entrance zone of the posterior roots at an amplification of 15 mm. per mV. Reflexes were recorded by isometric levers or in some cases electrically from a lead in the muscle.

Inhibition in the cat. Individual variations were too great to justify statistical treatment of the data. A few acutely spinal cats yielded inhibition curves of chronic pattern. We have never recorded an acute type of curve from a chronic cat. The dictum of Hughes and Gasser (2) that in the acutely spinal cat the presence of inhibition is associated with a positive wave in

* These results were reported at the Philadelphia Physiological Society, October 15, 1940 (8).

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the cord potential has proved valid for crossed as well as for ipsilateral inhibition (3) and for dogs and monkeys as well as for cats.

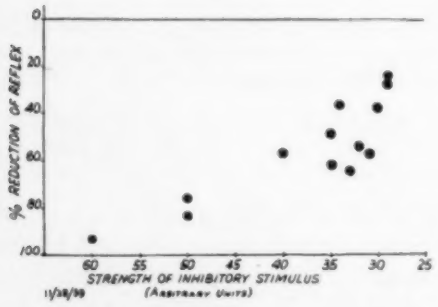

FIG. 1. Relation of strength of crossed inhibitory shock to degree of reflex inhibition at a constant interval of 46 msec in a cat 4–6 hr. after transection of the spinal cord. Excitatory shock to right sciatic nerve, constant strength (40 units). Inhibitory shock to left sciatic nerve; strengths indicated on abscissa. Ordinate indicates percentage reduction in contraction of right semitendinosus muscle. 11/28/39.

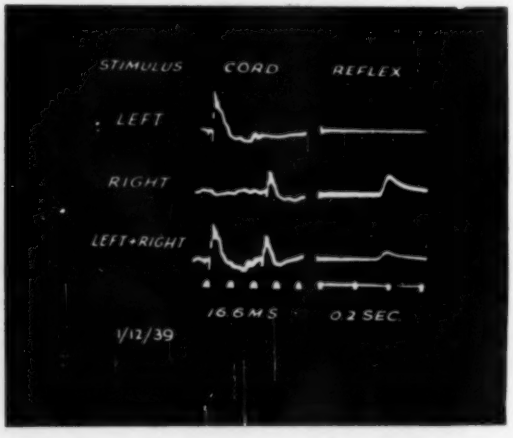

FIG. 3. Crossed inhibition of the flexor reflex without reduction of cord potential. *Macaca mulatta* 59 days after transection. 1/12/39. Stimulation of left and right peroneal nerves. Tension record from semitendinosus muscle.

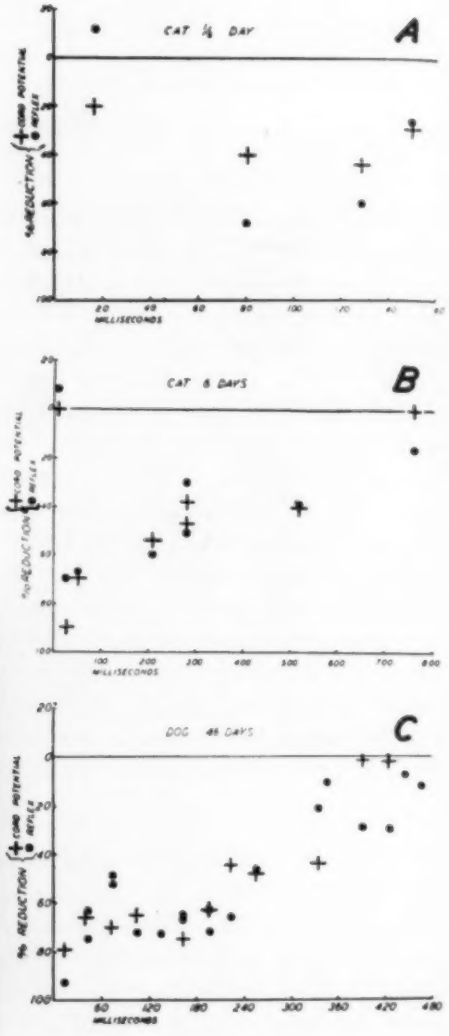

FIG. 2. Recovery curves of cord potential (plus signs) and reflex (dots) from crossed inhibition at various intervals after spinal transection: (a) cat 4 hours after transection; (b) cat 6 days after transection; (c) dog 46 days after transection.

In all three species the prominence of the positive wave of the cord potential (15) and the depth and duration of inhibition increase with the interval after transection. Thus in the acute cat a flexor reflex evoked by a

stimulus of twice reflex threshold strength is commonly inhibited by a crossed volley of four times threshold strength to a maximum depth of about 50 per cent of the test contraction, the inhibition persisting for less than a fifth of a second. In the chronic animal a conditioning volley of half this strength commonly induces complete inhibition which is still demonstrable after an entire second.

If inhibition be obtainable in the acutely spinal cat, it occurs after an inhibitory volley confined to alpha, beta, and gamma fibers. Occasionally a

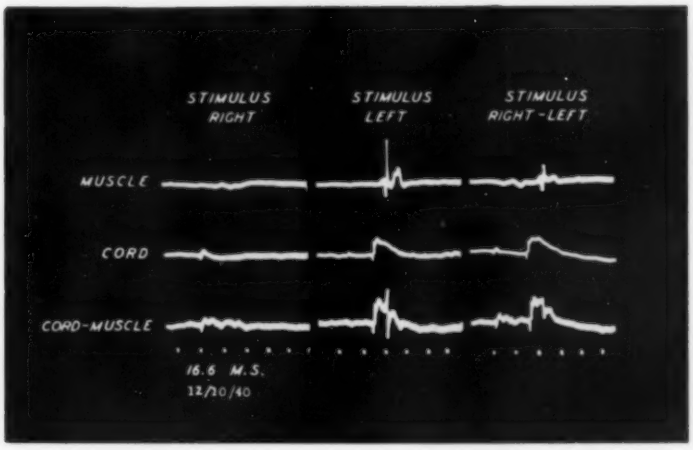

FIG. 4. Crossed inhibition of the flexor reflex without reduction of cord potential. *Macaca mulatta* 6 hr. after transection. 12/10/40. Top row, ground lead in semitendinosus muscle. Middle row, ground lead on cord. Bottom row, ground lead on cord, grid lead in semitendinosus; stimulating right and left posterior roots.

pronounced crossed inhibition of the flexor reflex may be conditioned by a stimulus scarcely above the threshold of the cord potential, involving only the fibers of lowest threshold in the alpha group. Within wide limits, the stronger the inhibitory shock, the deeper and more prolonged is the inhibition (14). The depth of inhibition at a constant interval of 46 msec. is plotted against the strength of the conditioning shock in Fig. 1.

In a previous paper (3) the parallelism in inhibition of the internuncial cord potential and the reflex response was emphasized. It is only in the chronic animal, however, that the two curves are identical. Acute cats usually show a somewhat deeper inhibition of the reflex response than of the cord potential (Fig. 2a). Though inhibition at the internuncial level accounts for the major share of reflex inhibition, this divergence of the two curves affords evidence in the acute preparation of some inhibition farther downstream.

Another feature of the pattern in the acute cat is facilitation at short intervals giving way at about 20 msec. to progressively deepening inhibition which reaches its greatest intensity between 30 and 60 msec. With increasing

chronicity this initial facilitation is curtailed and ultimately disappears (Fig. 2b and c). We are inclined to associate it with the crossed flexor reflex which recovers from spinal shock earlier than crossed extension only to suffer progressive eclipse as the latter reflex emerges from depression (9). These effects

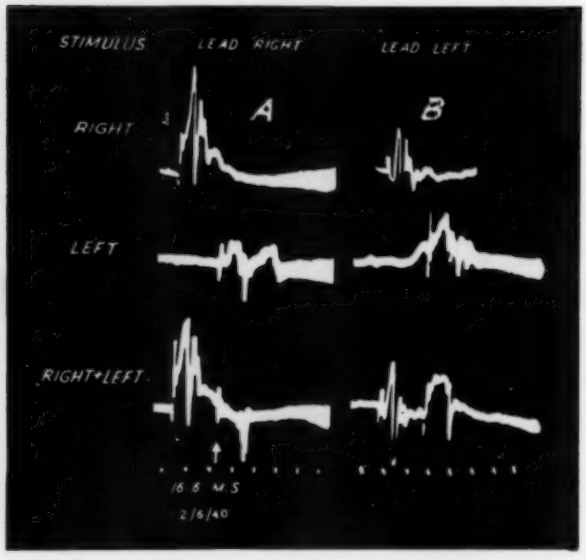

FIG. 5. Difference in the degree of crossed inhibition of the potential set up by a test volley in right and left dorsal horn regions respectively. *Macaca mulatta* 6 hours after transection. 2/6/40. Conditioning stimulus, right dorsal root, test stimulus, left dorsal root. (A) When the lead is from the dorsal horn on the same side (right) as the conditioning stimulus. (B) From the dorsal horn on the opposite side (left) to the conditioning stimulus

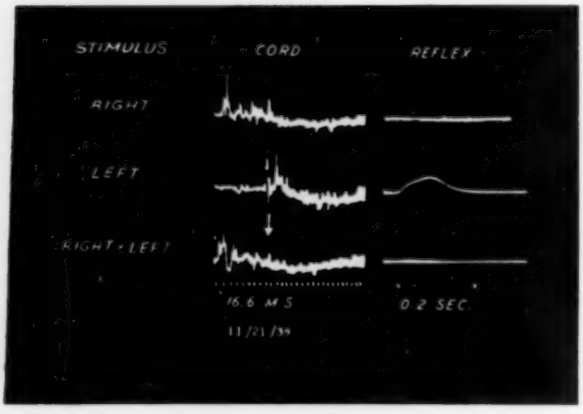

FIG. 6. Complete inhibition of cord potential and reflex, in *Macacus mordax* 36 days after transection. Excitatory stimulus, left external cutaneous nerve. Inhibitory stimulus, right external cutaneous nerve. Left semitendinosus muscle. 11/21/39.

of recovery from spinal shock are illustrated in the recovery curves comprising Fig. 2.

Inhibition in the monkey. In dog and monkey crossed inhibition is elicited only by stimuli far stronger than those which are effectual in the cat. In many acute monkeys it is unobtainable whatever the strength of the conditioning stimulus. Even in the chronic animal it is only by activating an appreciable number of delta fibers that we have obtained consistent results. In this regard, crossed inhibition differs from ipsilateral inhibition (10). It

reflects the increasing severity of spinal shock with ascent from lower to higher mammals.

A more important difference is in the stability of the internuncial cord potential. An instance in a chronic monkey of reflex inhibition without reduction in the internuncial potential has previously been reported (10) and is here reproduced as Fig. 3. In the acute monkey this is a not infrequent result (Fig. 4) and cases of deep reflex inhibition associated with only slight reduction of internuncial potential are common. In these with suitable grading of inhibitory and excitatory volleys, the crossed component of the internuncial potential from the excitatory volley proves to be more susceptible to inhibition than does the ipsilateral component (Fig. 5). It is only in the chronically spinal monkey in good condition that we have obtained reduction of corresponding degree of internuncial potential and reflex by a strong conditioning volley (Fig. 6 and 7).

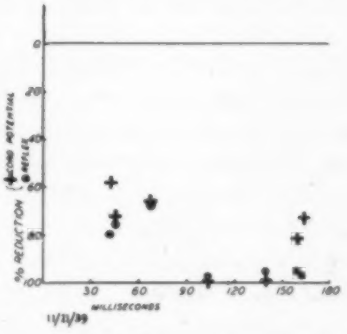

FIG. 7. Recovery curve indicating comparable degree of inhibition of cord potential and reflex in experiment illustrated in Fig. 9.

DISCUSSION

Van Harreveld (16) has recently reported that a brief period of ischemia of the spinal cord below the level of transection is followed by a more rapid reflex recovery than is transection without ischemia. He suggests that spinal shock may be due to inhibitory reflexes released from the control of higher centers; that such reflexes are especially susceptible to ischemia, which serves, therefore, to release excitatory reflexes from their control. His experimental approach and theoretical deduction are ingenious and accord well with one conspicuous result of lower thoracic transection in the decerebrate: the enhancement of rigidity in the forelimbs, presumably due to release from a source of inhibition below the level of transection (13). If spinal shock be due to inhibition, excitatory reflexes must be presumed to be more susceptible to inhibition during the period of their depression than after their recovery. In the case of the knee jerk this is actually the case (5). With the ipsilateral flexor reflex, however, the reverse is true. This reflex is less susceptible to either contralateral (Fig. 2) or ipsilateral inhibition (4) during the earlier than during the later phases of its recovery. Hence we incline to question the inhibitory source of depression of this reflex following spinal transection. If we seek to explain the difference in susceptibility between the knee jerk and the flexion reflex, one factor is obvious. Whatever the mechanism of spinal shock, it depresses extensor reflexes more severely than flexor. The source of inhibition of flexors experimentally available is part and parcel of the extensor reflexes which are so deeply depressed and *vice versa*. Reciprocal inhibition is depressed *pari passu* with the excitatory component with which it

is associated. The system behaves as though one and the same axon that supplies excitatory terminals to an extensor motoneuron furnished inhibitory endings to a flexor motoneuron. The result appears to be determined more by the availability of the inhibitor than by the susceptibility of the perikaryon to inhibition.

On the other hand, these results offer one bit of evidence pointing to increased susceptibility of perikarya to inhibition during spinal shock. In previous papers evidence was advanced for the conclusion that in the monkey motoneurons suffer deeper depression after transection of the cord than do interneurons (15, 4), and crossing interneurons deeper depression than unilateral ones (10). During spinal shock the monkey's motoneurons are susceptible to crossed inhibition at a stage when the less depressed interneurons resist it. With further recovery, the internuncial potential is also inhibited by a crossed volley. Presumably, in the earlier phase the crossed inhibition is too weak to affect the interneurons of the dorsal horn but does involve the depressed motoneurons. Later the crossing neurons recover to the point where a sufficient number discharge to inhibit the cells of the dorsal horn as well. The greater susceptibility to inhibition of the motoneurons may well be due to their depression by spinal shock. Such an argument hinges upon the assumption of relatively equal distribution of inhibitory endings of crossing neurons to cells of the anterior and those of the posterior horn. Beyond the suggestion from Cajal's finding of division of crossing fibers into two branches, one passing to the anterior, the other to the posterior horn (11) evidence for such an assumption is still lacking. Even if enhanced susceptibility to inhibition be admitted as a feature of spinal shock, it is not sufficient in magnitude to dominate the recovery curve of flexor motoneurons. On the contrary, the progressive deepening of inhibition of the flexor reflex with recovery from spinal shock impresses us as contrary to expectation on the basis of Van Harreveld's theory. Yet it is far from disproving his suggestion. It does imply, however, that the reflexes he postulates are not dominantly concerned with inhibition of flexor units. Such a conclusion accords with the high extensor tone of his animals.

To turn briefly to another aspect of our results, the case of the monkeys in which crossed reflex inhibition occurs without demonstrable change in internuncial potential is of interest in relation to current theories of inhibition. Such theories may be divided into those which refer the reduction in irritability to immediately preceding response of the same units and those which invoke specific inhibitory endings. If absence of demonstrable change in the intermediary cord potential be accepted as evidence that excitatory drive upon the motoneurons is not essentially altered, then it implies that inhibition has occurred in them in the absence of immediately preceding activity.

Figures 3 and 4 exemplify this situation. In each the cord potential is led from an electrode about 1.5 mm. in diameter on the surface of the cord close to the posterior root entrance zone on the side of the reflex response and

recorded at an amplification of 15 mm. per mV. We believe these records indicate internuncial activity throughout the dorsolateral quadrant of the cord at the level of maximum response to the test volley with sufficient sensitivity to be altered by any significant change in excitatory drive from interneurons which it engages.* In both cases the record of the cord potential from the test volley when preceded by a contralateral shock is identical with that of the unconditioned control. In both there is significant inhibition of the reflex response. Hence inhibition has occurred at the motoneurons which was not conditioned by preceding activity of the units involved.

A more direct proof of the same conclusion is offered by Lloyd (6). With a micro-electrode lead from the anterior horn of the cat under Dial anesthesia he made use of Renshaw's finding (12) on the basis of latency measurements that the initial reflex discharge is set up in response to activity of afferents ending directly upon anterior horn cells. He was able to inhibit this initial volley by a conditioning shock to an adjacent dorsal root.

Hence there are now two independent proofs of inhibition of motoneurons which is not conditioned by preceding activity of the inhibited cells. Since such inhibition has been demonstrated in both cat and monkey, it would seem probable that it has a general application. On the other hand, it does not follow that all inhibition is of this direct type. On the contrary, Lorente de Nó (7), Gasser (1), and others have advanced strong reasons for the existence of depression conditioned by preceding activity of the cell depressed. To this secondary type of inhibition it might be well to apply Dusser de Barenne's term, "extinction," reserving the name "inhibition" for the primary class of depression with which this paper deals. Such a distinction would place the primary type tentatively in the same category with the analogous case of peripheral inhibition in the autonomic nervous system, in relation to which the word was first employed.

Summary

Inhibition of the ipsilateral flexor reflex by a single afferent volley in a nerve or posterior root of the opposite side has been recorded in terms of the response of interneurons and of muscle in a series of cats, dogs, and monkeys at intervals after transection of the spinal cord ranging from a few minutes to two months.

In the cat crossed inhibition is obtainable with far weaker stimuli than in dog or monkey.

In all three species the depth and duration of crossed inhibition increases progressively with recovery from spinal shock. In all three, the chronic animal in good condition may show a corresponding inhibition of internuncial and reflex response.

* Though the occurrence of occasional interneurons in the anterior horn has been described their number is believed to be too small to alter significantly the internuncial drive.

The briefer the interval between transection and recording and the weaker the inhibitory stimulus, the more evident is a higher resistance to inhibition by interneurons than by motoneurons. In the cat this difference is insignificant and detectable only for a few hours after transection. In the monkey it is frequently extreme for a considerable period and has been demonstrated 59 days after transection.

These results are discussed in relation to the theory of the inhibitory genesis of spinal shock and in relation to the mechanism of inhibition. Evidence is presented for the occurrence of inhibition which is not conditioned by preceding activity of the inhibited neurons.

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CORTICAL ORIGIN AND DISTRIBUTION OF CORPUS CALLOSUM AND ANTERIOR COMMISSURE IN THE MONKEY (*MACACA MULATTA*)*

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THE CORPUS callosum and anterior commissure constitute a fibre system larger than the sum of all systems ascending to and descending from the cerebral hemispheres. Anatomical studies[1] and retrograde[32] and Wallerian[2,24–31,33,34,36] degenerations following lesions of this commissural system have indicated only cortical origins and axonal distributions which were for a large measure cortical and roughly symmetrical.

Little is known of its function. Apart from symptoms referable to lesions of adjacent structures,[35] tumors, softenings and surgical sections[38] have failed to produce any characteristic disorders except, possibly, impairment of coordination of the hemispheres in complicated symbolic activity.[35] Even complete transection of the corpus callosum has not invariably prevented the spread of convulsions from one side of the body to the other.[38]

Physiological results without electrical records were equally negative.[23] Bishop was probably the first to demonstrate a function referable to the corpus callosum. At the symposium of the American Neurological Association in 1937 he indicated that "when both occipital poles are released from domination by deeper structures, by cutting above the geniculate bodies, the corpus callosum throws these cortical areas of the two hemispheres into exact synchronism." In 1939 Erickson[21] found that section of the corpus callosum prevented the spread of electrical afterdischarge from one hemisphere to the other. In that same year, by stimulating one hemisphere electrically and recording from the other, Curtis and Bard[8] mapped the interhemispherical communications and, by sectioning the corpus callosum, they proved these to be by callosal fibres.

In 1937, while working on the functional organization of the sensory cortex of the monkey, Dr. Dusser de Barenne and one of the present authors had strychninized 1 sq. mm. of area 4 of one hemisphere and searched the other but found no strychnine spikes. When Curtis published his conclusive study the reason for the failure with strychnine was at once apparent, for the only strychninization had been in an area marked by him as having little or no callosal connection. One cannot hope, by local strychninization to discover any callosal connections which Curtis, by electrical stimulation, has not already disclosed, for strychnine acts only where synapses are present

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† National Research Council Fellow, 1940–1941.

on nerve cells and causes disturbances propagated only in the normal direction,[9,18] whereas we know no way to prevent electrical stimulation from producing antidromic disturbances and from exciting any axones passing through the stimulated area. It was, therefore, with the hope of clarifying and simplifying Curtis's findings, rather than of amplifying them, that the present study was undertaken.

METHODS

All experiments were performed upon monkeys (*Macaca mulatta*) fully anaesthetized with Dial* (0.45 cc. per kg., ½ intraperitoneal, ½ intramuscular). Both hemispheres were exposed widely, care being taken to preserve the cerebral circulation. For section of the corpus callosum, one side was prepared in advance by section of veins joining the brain to the superior longitudinal sinus. Thirty-six electrodes were placed on one hemisphere and connected, 6 at a time, to 5 channels of a Grass 6-channel inkwriter oscillograph. The arrangement was "linear" *i.e.*, successive channels had one electrode in common. The sixth channel was used for roving electrodes on the other hemisphere, and moved to the site of successive strychninizations. These were of about 10 sq. mm. so that the major portion of one hemisphere could be strychninized in each animal. When no spikes appeared at any of the 36 electrodes the area symmetrical to the strychninization was examined thoroughly by moving one or more electrodes from place to place over the area in question. Additional electrodes on the hemisphere strychninized were used to identify the site.

RESULTS

When one places on one hemisphere a small piece of filter paper moistened with a saturated solution of strychnine sulphate the surface of the cortex at the site of strychninization rapidly drifts negative and in less than half a minute there appear small fast negative fluctuations.[15] These cannot be detected except at the site of strychninization. Within about one minute a positive deflection precedes each negative fluctuation and a lesser and slower positive deflection follows. This is the fully developed strychnine spike, and it is propagated as a recognizable strychnine spike to all other regions reached by axones from the area strychninized. It was by means of

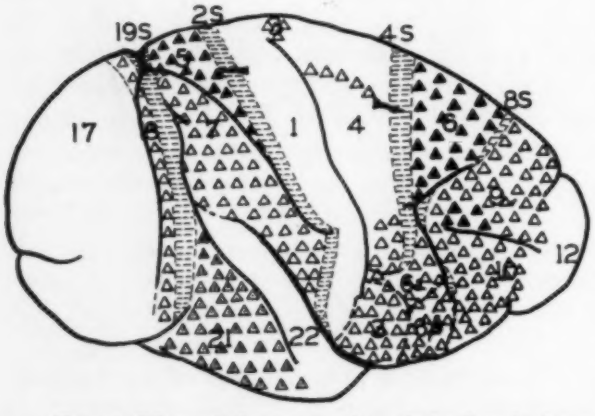


FIG. 1. Map of the convexity of the hemisphere numbered in conformity with Brodmann's nomenclature except for those numbers followed by S to indicate that these areas are identified by their giving suppression of electrical activity. They are indicated by horizontal shading.

△ = Projection to contralateral hemisphere at symmetrical focus only.

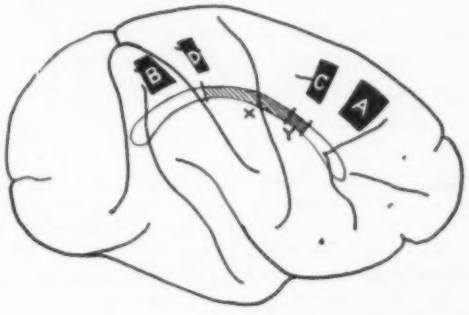
▲ = Projection to contralateral hemisphere at symmetrical and other foci.

◬ = Projection to contralateral hemisphere at symmetrical focus only which remains after section of the corpus callosum.

* We wish to thank the Ciba Co. for kindly putting the Dial at our disposal.

these strychnine spikes that the functional organization of the sensory and adjacent cortex[12] and of the occipital lobe[3] were originally mapped and found to conform in the main to the cytoarchitectonic maps of Brodmann[4] and the Vogts.[3,7] The map so produced formed the basis for the present experiments in determining what physiologically unique area was strychninized on one hemisphere or recorded on the other. Figure 1 shows such a map of the convexity of the hemisphere on which are plotted schematically the results of the present investigation.

In these experiments many minute, rounded or slightly belated disturbances of the opposite hemisphere were encountered. These have been consistently excluded in making Fig. 1, for it was feared that these might be electrical spread from structures other than those of the cortex subjacent to the electrodes (*e.g.*, fibre tract) or even postsynaptic disturbances. Thus, this diagram represents only the origin of indubitable commissural projections which pass from the cortex of the convexity of one hemisphere to the cortex of the convexity of the other without relay.



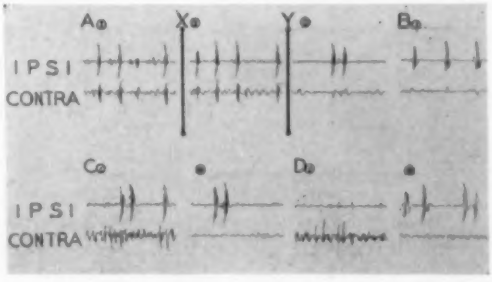


FIG. 2. Feb. 28, 1941. *Macaca mulatta*. Dial. Diagram of the convexity of the right hemisphere indicating sites of strychninization. On this is projected the corpus callosum indicating two partial sections thereof, X and Y. All records were made with bipolar pickup electrodes at the site of strychninization (ipsi) and on the contralateral symmetrical point (contra). Record A ① was made before section X; Record A ②, after section X but before section Y; Record A ③, after section Y. Records A ③ and B ① show the minute residual disturbances of the contralateral hemisphere. Records C ② and D ② show suppression of the electrical activity of the contralateral hemisphere.

None of the suppressor areas, 8s, 4s, 2s or 19s, gives rise to contralateral strychnine spikes, nor do areas 1, 12, 17 or 22. Area 9, except for a portion above the sulcus principalis, area 10, area 6a and b (face), area 4 (trunk, neck and face only), area 7, area 18 and area 21 give rise to contralateral disturbances restricted to foci symmetrical to the focus strychninized. Whereas part of area 9, above the sulcus principalis, area 6 (leg and arm) and area 5 (leg and arm) give rise to disturbances which are distributed to large areas of the opposite hemisphere. In fact, leg 6, arm 6, leg 5 and arm 5 give rise to disturbances of both pre- and postcentral sensory areas of the opposite hemisphere.

With one exception, section of the corpus callosum prevents the propagation of the strychnine spikes to the opposite hemisphere. Partial section pre-

vents their propagation from part of the hemisphere. Figure 2 shows diagrammatically such an experiment. Following a large strychninization, A, of area 6 of one hemisphere which was projected to the opposite hemisphere (Record A1) the corpus callosum was partially sectioned (cf. X in the diagram and at time X in the record). The strychnine spikes came through to the opposite hemisphere unaltered (Record A2). The section was then extended (cf. Y in the diagram and at time Y in the record). Then there remained only very small spikes (Record A3). Thereafter several strychninizations occipital to strychninization A were performed on areas known to have callosal projections, but no spikes appeared on the opposite hemisphere

FIG. 3. May 28, 1941. *Macaca mulatta*. Dial. Strychninization of entire left second temporal convolution, area 22, twenty minutes after complete transection of corpus callosum. Note strychnine spikes are largest in the record of the middle of the right second temporal convolution.

until strychnine was placed as far occipitally as B, which is in arm 7, when minute disturbances (Record B1) again appeared on the opposite hemisphere. Briefly, the section X+Y had interrupted almost all transmission via the corpus callosum from one sensory cortex to the other.

The exception mentioned above occurs in the case of area 21, the mid-temporal convolution. Strychninization in each part of this area resulted in typical spikes sharply restricted to the symmetrical focus of the opposite hemisphere. Section of the corpus callosum failed to prevent their occurrence. Figure 3 shows these spikes, as disclosed by the roving electrodes at the site and as recorded from the contralateral hemisphere. This strychninization covered practically the entire convolution and hence it is probably significant that the spikes on the contralateral hemisphere are larger and more constant in the middle third of the convolution than in either the anterior or posterior third. In this experiment the anterior commissure was intact.

In a second experiment it also was divided and thereafter no strychnine spikes were transmitted to the opposite hemisphere. Moreover, following section of the entire corpus callosum, electrical afterdischarge following

stimulation of area 21 on one hemisphere spread to the same area of the other hemisphere, and this spread was also prevented by section of the anterior commissure.

Suppression of the electrical activity of one hemisphere by strychninization of 8s, 4s, 2s and 19s of the other hemisphere has also been observed. This suppression has been obtained after section of the corpus callosum. Records C1, C2, D1 and D2 of Fig. 2 instance such suppressions of the activity of the contralateral hemisphere after strychninizations of 4s and 2s which lie within an area all of whose callosal connections had already been severed.

Discussion

The known anatomy and physiology of the corpus callosum and anterior commissure and the known properties of the strychnine spike would lead one to expect at least all the positive findings of direct interhemispherical connection here presented. In fact, these constitute, so far as the callosal system is concerned, a partial confirmation of those of Curtis,[5] from which they differ only privatively. Due to the relatively large strychninizations and the large number of foci recorded following each strychninization it is not likely that the differences are due to oversight. It is possible that potentials which were regarded as of questionable significance, and so excluded from Fig. 1, would have been included by Curtis as small disturbances, but certainly the greatest reason for the differences must be sought in the dissimilarity of stimulation. Such positive findings of commissural connections as are obtained by its use indicate cell bodies which are situated in the area strychninized and give rise to axones extending to the site of appearance of the strychnine spikes. From the voltage of these spikes it is highly probable that many axones must participate, although it is impossible to say how many. Systematic exclusion of small and questionable disturbances may well have prevented indication of callosal connections which were comparatively scattered and not numerous. Thus Fig. 1 is in no sense a complete chart of interhemispherical connections but merely a diagram of the lateral aspect of one hemisphere on which are indicated those of its areas which give rise to numerous callosal axones ending in the cortex of the convexity of the opposite hemisphere. As less than one-sixth of the total cortex of one hemisphere is on the surface of the convexity Fig. 1 cannot represent more than one-sixth and may represent as little as one thirty-sixth of the total area giving axones to the commissural system.

The primary projection areas of vision and of somatic sensation are markedly deficient in callosal projections whereas so-called associational areas have them in abundance. Similarly when one looks at the primary motor area, 4, one finds these callosal connections restricted to areas controlling parts of the soma which are most frequently used symmetrically, and lacking from those representing the extremities which are moved independently. On the motor side of the sulcus centralis the greatest callosal projection arises

from areas leg 6 and arm 6 whose stimulation yields more complex movements.

That section of the corpus callosum failed to prevent firing of one area 21 by the other, and that this firing occurred without time for relay in other

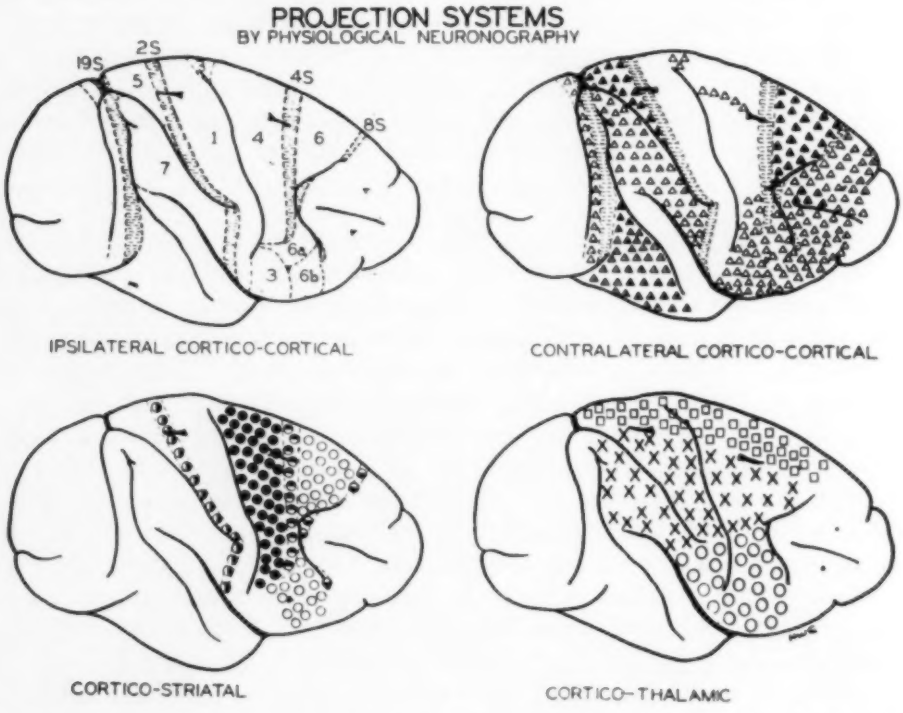


FIG. 4. Numbers indicate portions of the sensory and adjacent cortex distinguished on the basis of their firing into other areas or being fired into from other areas of the same hemisphere except those numbers followed by S which yield suppression of electrical activity of the cortex. Horizontal shading indicates areas identified by suppression.

△ = Projection to contralateral hemisphere at symmetrical focus only.
▲ = Projection to contralateral hemisphere at symmetrical and other foci.
◬ = Projection to contralateral hemisphere at symmetrical focus only which remains after section of the corpus callosum.
◑ = Projection from area 2s to nucleus caudatus.
● = Projection to putamen.
◓ = Projection from area 4s to nucleus caudatus.
○ = Projection to putamen and to external segment of globus pallidus.
◒ = Projection from area 8s to nucleus caudatus.
□ = Projection to leg nuclei of the thalamus.
× = Projection to arm nuclei of the thalamus.
○ = Projection to face nuclei of the thalamus.

structures indicates that cells situated in area 21 have axones passing to the other hemisphere by a bridge other than the corpus callosum. Anatomical considerations by exclusion strongly indicate that this must be by way of the anterior commissure—a conclusion confirmed by failure to cross following section of the anterior commissure.

Since it is clear from previous work of this laboratory,[14] and from Erickson's study,[21] that electrical after discharge (and therefore the central disturbance in clonic seizures) spreads by neuronal paths it is to be expected that section of the corpus callosum alone would prevent the spread of many seizures from one side to the other. The remaining connection of the areas 21, by way of the anterior commissure, should suffice for the crossing if the disturbance spread to the temporal lobe on the first side. Erickson[21] had not investigated these regions from, and to which crossing occurs via the anterior commissure. As shown by the present findings of spread of after discharge, these may play a significant role in those patients of whom Van Wagenen[38] reports that they had seizures recurring bilaterally after section of the corpus callosum. Thus, apart from its surgical implication, this finding concerning the anterior commissure is significant in explaining the apparent contradiction between Erickson's conclusions and Van Wagenen's reports.

Two new findings with respect to the suppressor areas—(i) that suppression of electrical activity is bilateral, (ii) that it remains bilateral after section of the corpus callosum—are in harmony with conclusions from previous experiments.[13,16] Since the path responsible for suppression of electrical activity is known to be subcortical and the effect is bilateral, and since suppression of motor response [17,19] to cortical stimulation is necessarily subcortical, and bilateral, the third finding is not surprising—namely, that the areas (8s, 4s, 2s and 19s) responsible for these suppressions give rise to no demonstrable callosal projection.

Curtis has already called attention to the failure of the callosal system to correspond to cytoarchitectonic or somatotopic subdivision of the cortex.[5] Figure 4 amplifies this point by contrasting four maps of the convexity of the hemisphere as so far revealed by physiological neuronography. The upper left shows how that cortex can be divided on the basis of corticocortical connections.[3,12,14,20,22] The suppressor areas (8s, 4s, 2s and 19s) lack such connections. The upper right shows the principal origins of the corpus callosum and anterior commissure. Again the suppressor areas lack those connections. The lower left shows the areas separated on the basis of their projection to basal ganglia.[13,16] Here all half-filled circles indicate connections to the nucleus caudatus. All come from the suppressor areas, and stimulation of the nucleus caudatus yields suppression. The lower right indicates origins of the essentially somatotopic projections to the leg, arm and face nuclei of the thalamus.[10,11] Thus, this figure reveals the unique origin of each of these systems. The corpus callosum and anterior commissure are no exceptions.

Conclusions

Based on local strychninization of one hemisphere and electrical records of the other, *i.e.*, by physiological neuronography, a new map of the convexity of the cerebral hemisphere of *Macaca mulatta* has been prepared to show the origins of the corpus callosum and anterior commissure and to indicate (i) those origins whose interhemispherical projections are dispersed to

many areas of the convexity of the other hemisphere, and (ii) those whose projections are restricted to symmetrical foci.

The former spring from a part of area 9 above the sulcus principalis and from areas 5 and 6 of the leg- and arm-subdivisions. The latter have been found to arise from many parts of the frontal pole, from face 6, from the trunk and face portions of area 4 and from areas 18 and 21.

The last of these restrictedly symmetrical projections, *i.e.*, that between the areas 21, is unique, for it alone remains after section of the corpus callosum, provided the anterior commissure is intact.

Suppression of electrical activity of the cortex by strychninization of 8s 4s, 2s or 19s has been found to be always bilateral, even after section of the corpus callosum to which these areas contribute few or no axones.

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CORTICAL ORIGIN AND DISTRIBUTION OF CORPUS CALLOSUM AND ANTERIOR COMMISSURE IN CHIMPANZEE (*PAN SATYRUS*)*

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THE interhemispherical communications of the sensory cortex have been investigated in the same manner and often in the same animals as the functional organization of the hemispheres separately,[8,11] *i.e.*, by the local application of strychnine and the recording of the resultant alteration of electrical activity. Because those studies of the sensory cortex had shown that the investigation had to be extended not only to adjacent[1] but even to remote[2] parts of the same hemisphere these were also strychninized and recorded on both hemispheres. Finally, in view of what had already been found concerning the temporal lobe and the anterior commissure in the monkey,[15] this region was also investigated before and after section of the corpus callosum. Thus, these experiments have extended step by step to include the entire convexity of the hemispheres. Since these findings all pertain to the commissural system which subserves a relatively distinct type of functional organization, they are presented separately in this article.

METHODS

The experiments were performed upon six chimpanzees (*Pan satyrus*) fully anaesthetized with Dial§ (0.35 cc. per kg., ½ intraperitoneal, ½ intramuscular). Both hemispheres were exposed by turning down large bone flaps. For experiments on the temporal region and on the temporo-parietal angle the zygomatic arches and the temporal muscles were removed and the temporal bones cut back as far as vascular structures permitted. For investigation of the orbital surface of the frontal lobe the orbit was exenterated and its bony roof removed. Previous to sections of the corpus callosum and anterior commissure the sagittal arch between the bone flaps was removed and the vascular attachments of one hemisphere to the longitudinal sinus and the falx were cauterized and severed. Sections of the commissural systems were made with a blunt instrument and no bleeding was encountered. By so tipping the board to which the animal was attached that the heart was level with the head, by carefully preserving all vessels that did not have to be severed, and by avoiding trauma to the arachnoid membrane so that the cerebrospinal fluid did not escape, the cortex was kept in good condition without irrigation for an exposure lasting as long as three days.

Twelve electrodes were applied to the hemisphere to be strychninized and thirty-six to the other. By appropriate switching, six of these at a time were connected in the "linear" hook-up to five channels of a 6-channel Grass inkwriting oscillograph. The sixth channel was used for roving electrodes at the site of strychninization. In several experiments strychninizations were performed on the hemisphere with the thirty-six electrodes to work out

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‡ National Research Council Fellow, 1940–1941.

§ We wish to thank the Ciba Co. for kindly putting the Dial at our disposal.

details of its functional organization and thus to define the location of these electrodes. In such cases the other twelve electrodes were moved about to locate strychnine spikes on the hemisphere contralateral to the strychninization. Over 200 relatively large strychninizations with the recording of upward of 40 foci in each case have made it possible to investigate the entire convexity of the hemispheres for origins and terminations of the commissural systems.

Results

These observations on the commissural system were made during investigations of the sensory and adjacent cortex of the convexity of the hemisphere. The functionally unique bands revealed by that study served to locate both strychninizations and electrodes. These were plotted for each animal and then a generalized map was made.[11] Figure 1 is such a map on

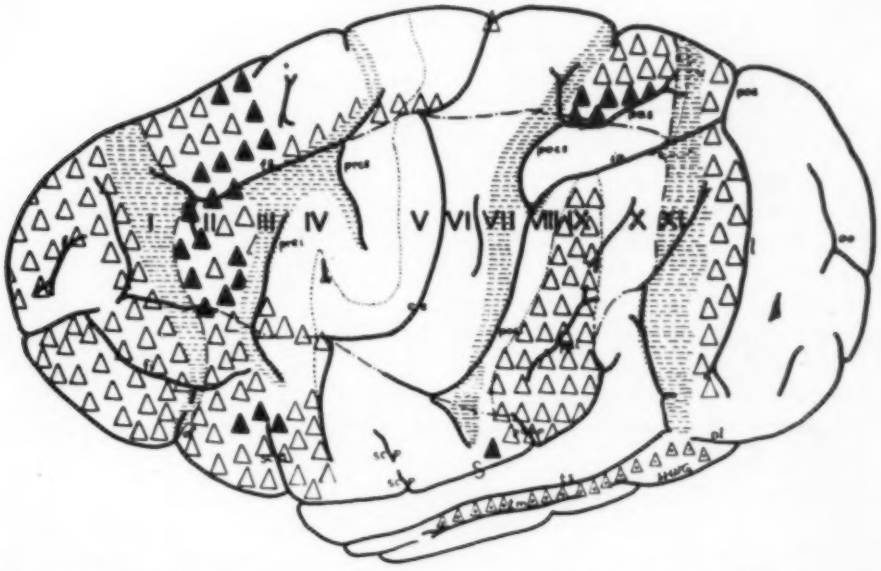

Fig. 1. Numerals refer to physiologically unique bands of sensory and adjacent cortex. Shading indicates suppressor areas.
△ = Origins of restrictedly symmetrical disturbances.
▲ = Origins of disturbances of symmetrical and more widespread disturbances of the contralateral hemisphere.
◬ = Origin of symmetrical disturbances persisting after section of corpus callosum.

which the triangles indicate the sites of strychninizations which resulted in large and typical strychnine spikes appearing promptly on the contralateral hemisphere. This is a general map and it is not possible to homologize exactly even the two hemispheres of a single chimpanzee. Therefore, an empty triangle symbolizes not one strychninization, but the approximate site of several, each of which fires only to a symmetrical focus and, similarly, a filled triangle indicates the approximate site of several, each of which fired to other areas of the contralateral hemisphere as well as to its symmetrical opposite. The suppressor areas, indicated by shading, and the remaining areas, unmarked

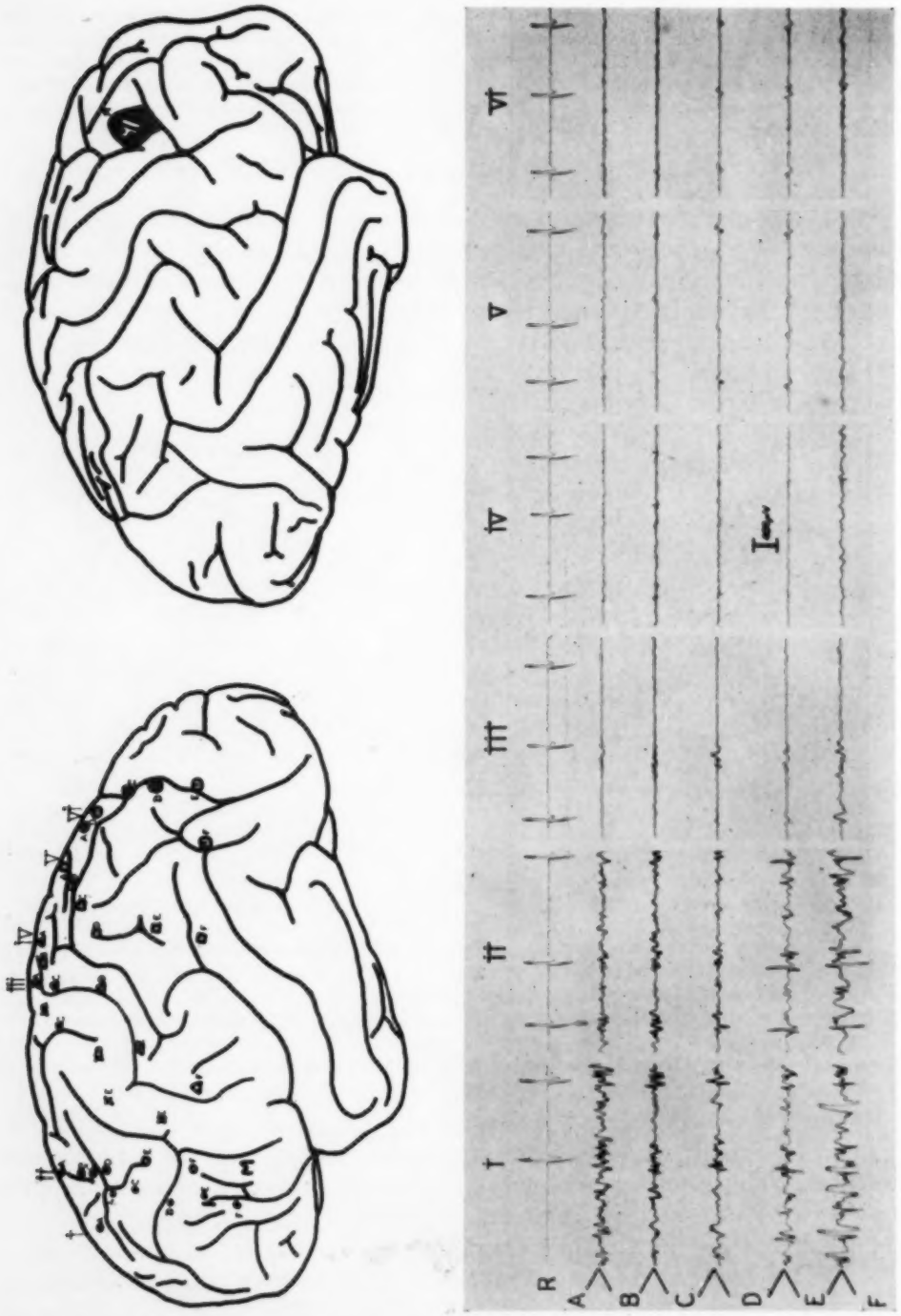

FIG. 2. May 27–28, 1941. Chimpanzee XVIII. Dial. Strychninization of anterior margin of Band II. Right hemisphere. Diagram indicates location of same with adjacent rover electrode and location of electrodes on opposite hemisphere. Records show large strychnine spikes at symmetrical focus and smaller ones in neighboring areas. Also small disturbances in posterior part of sensory cortex and in vicinity of sulcus lunatus.

in the figure, were all strychninized but gave rise to no certain or recognizable contralateral strychnine spikes.

Obviously, this figure fails to indicate the termination of commissural systems which fire other areas in addition to the symmetrical focus. Both such areas in the postcentral cortex cross only into the postcentral cortex. The upper, in the superior parietal lobule, is distributed to Band IX, leg, trunk, arm and face; the lower, in the lower end of the postcentral convolution, into Bands VIII and IX, face and arm.

The widest contralateral distribution is from Band II. All parts of this band fire to symmetrical foci and all solid triangles are at places which fired to other subdivisions, leg, arm or face, of Band II contralaterally. Moreover, strychninizations in each of these subdivisions of Band II produced contralateral firing of more than one subdivision of Band IV and sometimes, though only questionably, of Band V. All subdivisions of Band II have also fired into some postcentral portion of the opposite sensory cortex. This firing was most limited from face II, which fired face VI and from trunk II, which fired only one part of arm X; next, from leg II which fired into the gyrus above the sulcus interparietalis, presumably trunk VIII and IX, as well as into leg and arm IV; and, least restricted, from arm II, which fired into all of the areas affected by leg II and also into the anterior lip of the sulcus lunatus. Figure 2 exemplifies this finding.

With one exception, all firing of the hemisphere contralateral to the strychninization ceased when the corpus callosum was divided. This exception was found in the temporal lobes where strychninization of the middle and posterior thirds of the second temporal convolution still fired symmetrically after, although at a lower voltage than before, the section (see Fig. 1).

Following strychninization of each of the suppressor bands (see Fig. 1) bilateral suppression of electrical activity of the cortex has been observed. The activity diminished in corresponding areas at approximately the same time on the two sides but, as the electrodes were not arranged for simultaneous records, with the one exception of the rover, discrepancies of less than one minute could not have been detected (see Fig. 3). These suppressions remained bilateral after section of the corpus callosum.

Discussion

The topography of the chimpanzee's cortex is very variable and the present report is based on only 6 chimpanzees—a total of only 223 strychninizations. Moreover, the cortex of the chimpanzee is so large and so functionally differentiated, and the area which shows a contralateral strychnine spike can be so small even when the strychninized area is relatively large, that 36 stationary electrodes are far too few for an exhaustive survey of even a restricted area such as the frontal lobe or the temporal lobe or the sensory cortex. Although these electrodes were supplemented by frequent attempts to locate symmetrical disturbances by moving electrodes many disturbances, particularly if they involved only small, unsymmetrical areas, may have been

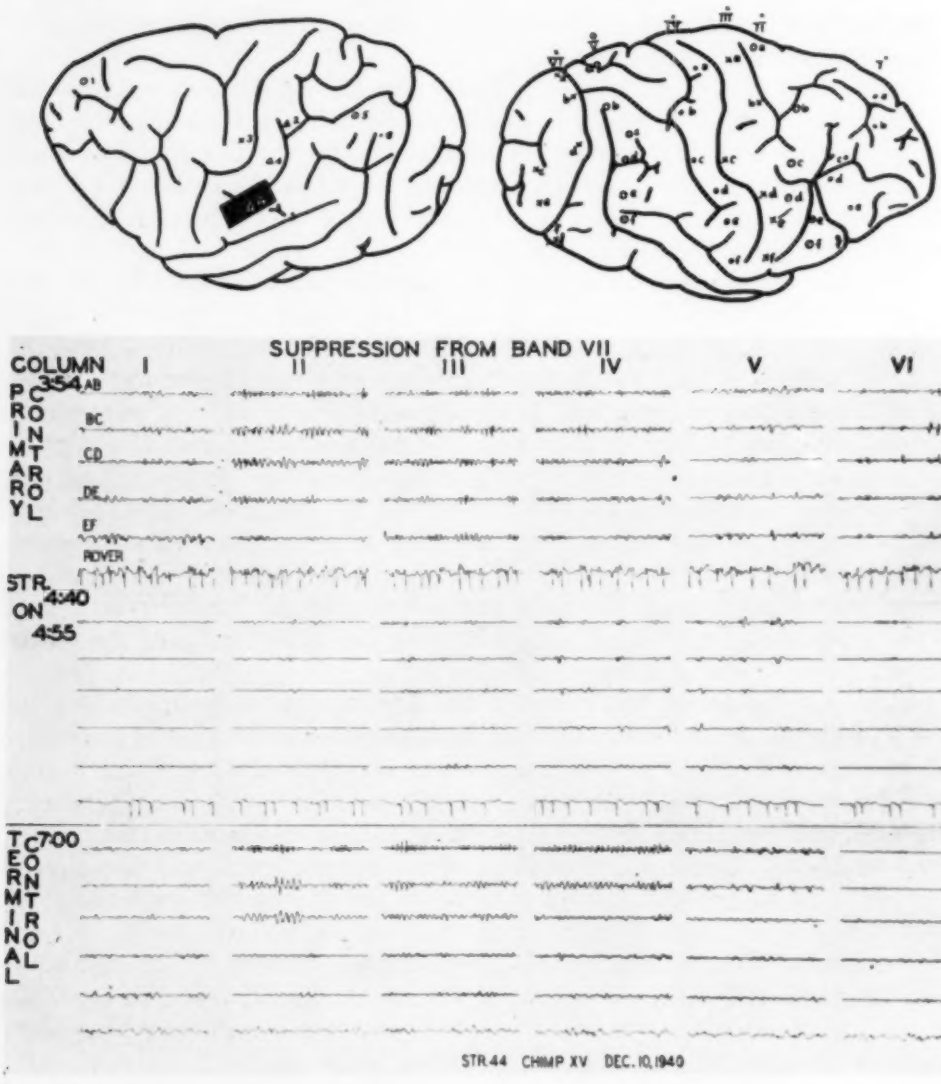

FIG. 3. Dec. 10, 1940. Chimpanzee XV. Dial. Strychninization number 44. Diagrams of location of strychnine and electrodes in the most prolonged suppression of the contralateral hemisphere as yet seen in the chimpanzee. After primary control rover moved from site of previous strychninization to that of strychnine 44. Note—activity not fully returned in 2 hours 20 minutes.

missed. For this reason, as well as for those stated in the articles on the commissural systems of the cat[15] and the monkey,[16] the map of the lateral aspect of the chimpanzee's cortex showing the origin of callosal systems must be regarded as incomplete. It indicates only the chief origins of the callosal system which lie on the convexity of the hemisphere and terminate in a relatively concentrated manner upon the convexity of the opposite hemisphere.

During these studies it has become increasingly apparent that Curtis[4,5,6] and Curtis and Bard[7] were correct in their description of the extremely circumscribed, exactly symmetrical, type of contralateral representation. This functional commissural connection is far more precise and restricted than is suggested by the term "homeotopic" used to describe the corresponding anatomical connections. Moreover, in every case we have confirmed their finding of symmetrical firing even when the origin excited fired widely distributed areas of the contralateral hemisphere. This must mean anatomically that with every heterotopic is intimately associated a homeotopic callosal connection. The association seems to be due to the fine structure of the brain rather than to excitation of adjacent but dissimilar areas, for it was found by Curtis with electrical stimulation near threshold strength, and by the present authors with the smallest strychninization.

This is only one of several noteworthy points of similarity in these studies of cat, monkey and chimpanzee. Several need only be mentioned, such as the failure to discover any commissural connections from any suppressor areas, from those parts of area 4 which control parts of the body used most independently (*i.e.*, leg 4 and arm 4) and from area 17. While there is no satisfactory chart of the cytoarchitecture of the chimpanzee, if one homologizes on the basis of functional organization,[1,9–14] and uses Brodmann's numbers[3] throughout it is possible to state some of the remaining similarities briefly Area 18 and part of area 3 and at least some part of the face-subdivision of area 4 yield in each animal restrictedly symmetrical disturbances which are entirely mediated by the corpus callosum, whereas area 21, which has such a projection, utilizes, in part at least, the anterior commissure. Finally, while the widespread disturbances are encountered only from restricted portions of the cortex which are neither "motor" nor" sensory"[17] in the most restricted sense, these origins do not lie in the newer associative areas nor enlarge as these enlarge. Unfortunately area 6 was not investigated in the cat, but in both the monkey and the chimpanzee it is the source of the widest callosally mediated disturbances. Similarly area 5 gives rise to widespread contralateral disturbances, although not to as remote areas. In the cat, the part of area 7 adjacent to area 5 has similar properties. In the monkey this area has only origins of symmetrical disturbances, and in the chimpanzee in which "area 7" has either further differentiated or been invaded by newer association areas, only part of the region has origins of the restrictedly symmetrical type, and the rest, none. This may be a development comparable to the differentiation in the face region in front of the Rolandic fissure where, in the chimpanzee, the upper half of the face region no longer gives rise to any discoverable commissural system, although the neck region (above) and the lower face region (below) have such connections.

Three other small areas gave dissimilar findings in monkey and chimpanzee but the authors have no way of knowing whether these are due to areas being in the depths of a sulcus in one animal and on the convexity of a convolution in the other, or to changes comparable to those in "area 7".

The first is found above the sulcus principalis in area 9 of the monkey, and the other two appear in the chimpanzee, one just in front of the lower part of Band IV in the face-subdivision, and the other just above the Sylvian fissure below and behind the end of the sulcus interparietalis. In this connection it should be added that the longest projection from the frontal margin of the arm-subdivision of area 6 (Band II) to the contralateral area 18, was found in the chimpanzee, but diligent search failed to reveal it in the monkey, in whose cortex arm 6, where it adjoins area 8, dips into the sulcus arcuatus. Thus these discrepancies may merely be examples of the incompleteness of our knowledge, due to failure to excite the origin or record the termination of the part of the commissural system under investigation.

It must, finally, be emphasized that these studies are complementary to those on the functional organization of one hemisphere and no attempt has been made to detect anything except origins and terminations which are cortical.[18]

Conclusions

By local strychninizations of one hemisphere and recording electrical activity of both, a new schematic map of the convexity of the hemisphere of *Pan satyrus* has been made to indicate the principal origins of the corpus callosum and anterior commissure. It shows (i) those origins of commissural fibers which project to many areas on the convexity of the other hemisphere and (ii) those which project only to symmetrical foci. The former arise from all subdivisions of Band II and from two small areas, one above the superior parietal sulcus and the other below and behind the inferior extremity of the interparietal sulcus. The latter come from many regions of the frontal pole, from scattered parts of Band II, from the trunk, neck and lower face regions of Bands IV and V, from Band IX and from a region adjacent to the sulcus lunatus (presumably area 18) and from the central and posterior thirds of the second temporal convolution (probably area 21).

The last of these origins is unique in that strychnine spikes continue to be propagated (although at reduced amplitude) to the symmetrical focus following section of the corpus callosum and, hence, it must give rise to axones which are to be sought in the anterior commissure.

Suppression of electrical activity of the cortex by strychninization of Band I, III, VII or XI has been found to be bilateral even after section of the corpus callosum to which these bands contribute either no axones or too few to yield a recognizable strychnine spike.

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POTASSIUM AND WATER CHANGES IN EXCISED NERVE ON STIMULATION

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FENN (1940) has discussed the now generally recognized loss of potassium by glands, muscles and nerves, during activity. In unmyelinated crab nerves a clear loss has been shown by Cowan (1934) and Young (1938). They produced changes of 6–7 per cent after 5–15 minutes of electrical stimulation. On the other hand, Fenn (1934, 1938) found no significant changes after stimulation of the myelinated nerves of frogs and cats. The question is still open therefore whether myelinated nerves are an exception to the general rule or whether they can be made to lose potassium under proper conditions.

The above mentioned investigators generally employed stimulation periods of 30 min. at most, and did not test the response of the nerves directly. This paper shows that excitation of myelinated frog nerve must be continued for more than 30 min. before any change is evident. Fenn (1934) did apply tetanizing currents to frog nerves for as much as 6 hours, with a consequent loss of K, but his experiments were too few to be significant.

In our work, the stimulation times ranged from 13 min. to 3.5 hr. The response of the nerves was followed by measuring the height of the diphasic action potentials on a cathode ray tube.

METHOD

The sciatic nerves of two frogs were used for each experiment. After equilibration for at least two hours in Ringer's solution‡ at 5°C., one pair (S pair) was placed in 1.2 cc. of the solution in the stimulating chamber (S chamber). This consisted of a narrow groove cut into a paraffin block, covered with a glass plate. At one end of the groove, a closely-spaced pair of platinized electrodes was used for stimulation, and a similar pair at the opposite end was used for recording. The electrodes were separated from the middle part of the groove by partitions, and the salt solution was confined to this central part. Air was bubbled through the bath, after first passing through an external reservoir of the same solution.

The main body of the nerve-pair was immersed in the central part of the groove; the nerve ends were drawn out of the bath, across the partitions, and placed on the electrodes. Thus the electrodes were kept in air, and the stimuli did not pass through the fluid and the whole nerve trunk, as was the case in Cowan's procedure (1934). The stimuli were slightly supramaximal thyratron-controlled condenser discharges, adjusted to 60 per sec. in all trials.

After stimulation, the nerve ends which had projected beyond the bath were cut off and the remainder of the trunk was analyzed for potassium. The analyses were made by

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‡ Composition, in gr. per liter solution: NaCl 6.5, KCl 0.14, $CaCl_2$ 0.12, $NaHCO_3$ 0.20, NaH_2PO 0.01. Total K, including impurities, =0.074 mg/cc. solution.

W.S.W. using a modified Shohl and Bennett method (Wilde, 1939). Amounts of K as small as 0.035 mg. were measured with an average variation of ±1.5 per cent.

A separate chamber (C chamber), identical with the S chamber, was provided for the control nerves (C nerves). For each experiment, a pair of C nerves was run simultaneously with the S nerves, though only the latter were stimulated. The response of the controls in groups A and B was measured by giving them a few test shocks at the beginning of a run, and again at the end. The potentials of these controls showed no deterioration during any of the runs.

Results and Discussion

Changes during activity. Table 1 consists of the original data, separated into 3 parts according to the duration of stimulation. No nerves were stimulated in the third group. These tests simply provided an additional check on the method of selection, which was as follows: the right sciatic of one frog and the left sciatic of a second frog were used for stimulation. The remaining two nerves were used as controls.

In the last 7 experiments of Table 1 this procedure was followed as usual, except that the nerves in the S chamber were not stimulated. There was no significant difference between these and the C nerves in regard to either K or water (group C, Table 2). There was still no definite change in group B, activated for 13–30 min., but group A, activated for 60–210 min., showed a loss of K without any corresponding shift in water (unaltered dry weight).

In two of the tests (12, 14) the movements of K were followed by analysis of the bath as well as the nerves. In each case the rise of K in the fluid indicated a loss of 18–20 mg. per cent per hr. by the stimulated nerves. This agreed with the values of 14–20 mg. per cent per hr. shown by direct analysis of the nerves. In fact, all the trials in the first group (60–210 min.) showed losses during activity within a range of 10–20 mg. per cent per hour, with the exception of the two showing gains (no. 3, 13).

Cowan's results are in sharp contrast (1934). He reported a leak of about 180 mg. per cent per hr. from the unmyelinated nerves of crabs as a result of stimulation. However, stimulation was continued for only 10 min. It would be of interest to see how long the rate of loss could be maintained.

The smaller change in frog nerve may be due to the myelin sheath. The sheath seems to be impermeable to electrolytes, considering the high internodal resistance recorded by Tasaki (1939). The high conductivity at the nodes suggests that this might be the only place where K can escape. Erlanger and Blair (1938) offer additional evidence in support of this view. They state that isotonic glucose blocks frog nerve by reducing axon excitability at the nodes, where K presumably leaks out.

Changes during soaking. Table 3 shows the difference between short and long soaking on the K and water contents of the C nerves. Prolonged immersion caused a definite drop in the dry weight fraction, indicating a gain of 9.5 per cent in the amount of water associated with each 100 gm. of dry weight.

Prolonged immersion also resulted in a fall in concentration of K in nerve water. However, the concentration in dry nerve was not significantly

Table 1. Analytical data

Exp.	Mg. wet nerve		Per cent dry weight		Mg. per cent K in wet nerve		ΔK wet per cent	Stim. min.	Final potential per cent	Temp. °C.	Soaking hr.
	C	S	C	S	C	S					
Group A—Long Stimulation											
1	31.7	32.4	26.8	26.5	227	176	−22.5	210	50	25	5
6	20.9	23.1	23.9	29	187	156	−16.6	184	25	15	5
12	24.6	26.4	24.8	24.6	219	170	−22.4	154	40	15	10
14	38.8	41.6	27.1	26.4	183	151	−17.5	140	71	23	100
5	20.2	19.1	32.2	44	307	272	−11.4	139	33	15	5
4	37.3	37.4	28.4	28.6	236	208	−11.9	110	46	25	20
13	45.7	41.9	26	24.8	173	184	+ 6.4	90	34	16	10
2	35.6	34.4	26.4	30.5	222	209	− 5.9	85	77	26	2
3	44.4	46.6	25.2	26	180	184	+ 2.2	75	50	25	20
11	—	25.4	—	25.6	—	197	(−27.5)	60	47	16	40
Group B—Short Stimulation											
15	34.7	36	25.4	27.2	210	189	−10	30	90	29	25
16	40.3	38	28	28.7	213	245	+15	30	93	29	10
17	34.5	33.7	28.1	28.8	203	234	+15.3	30	90	29	10
18	36.6	37	27.1	27	218	221	+ 1.4	30	83	29	2
19	35	32.1	24	26.2	214	209	− 2.3	30	82	29	20
20	34.5	35.2	27.3	29	223	210	− 5.8	30	87	29	20
21	30.4	29.9	28.3	24.8	207	184	−11.1	30	88	29	30
22	30.3	31.3	27	23	214	198	− 7.5	30	82	29	30
23	30.7	30.5	27.1	27.2	234	213	− 9	30	91	29	25
24	28.7	29.3	25.8	24.9	223	211	− 5.4	30	96	29	25
10	24.8	24.7	27.8	27.5	238	231	− 2.9	30	63	16	5
7	39	38	28	28.7	208	210	+ 1	13	57	14	2
9	48.5	50.3	25.4	25.7	194	199	+ 2.6	13	69	16	15
Group C—No Stimulation											
8	37.7	36.6	25.5	26.2	228	221	− 3.1	—	—	28	15
25	24.2	22.4	24.8	26.3	206	227	+10.2	—	—	28	15
26	42.2	44.8	26.3	27.7	220	214	− 2.7	—	—	28	2
27	28.9	27.7	30.4	28.2	214	231	+ 7.9	—	—	28	2
28	36.4	36.2	24.7	22.7	198	204	+ 3	—	—	28	30
29	31	30.7	23.2	24.1	200	202	+ 1	—	—	28	30
30	47.4	44.2	22.2	23.5	192	203	+ 5.7	—	—	28	20

C—control nerves. S—stimulated nerves. The final column refers to the soaking of control nerves only, during equilibration and control periods combined. In exp. 11 the control nerve was lost; the change in potassium was determined by analysis of the Ringer bath; in all other instances, $\Delta K = (S - C/C) \times 100$. The final group of 7 experiments provides a check on the method of selection; the nerves in the "S" columns were not actually stimulated. The final potential was measured in per cent of the initial value obtained at the onset of stimulation; figures are given for the "S" nerves only.

altered. The loss of K calculated on the basis of nerve water must then be only an apparent one. The real change is evidently a gain of water, resulting in a decrease of the dry weight fraction.

Although Table 3 shows no further loss of K after 2–5 hr. of soaking there is evidence of a small loss from resting nerve during this shorter period, as shown by an increase in K concentration in the bath in 3 cases (11, 12, 14) in which analyses were made. The losses recorded per hour were 1 mg. per cent for 100 hr. (no. 14); 2 mg. per cent for 40 hr. (no. 11); and 4 mg. per cent for 10 hr. (no. 12). Presumably most of this loss occurred in the first

Table 2. Average per cent changes due to stimulation

Group	No. of cases	Stim. min.	K in wet nerve	K in dry nerve	K in nerve water	Nerve dry weight
A	8	60–210	−11.0 ±2.6	−13.7 ±3.2	−9.6 ±2.7	+4. ±2.2
B	13	13–30	− 1.4 ±1.6	− 1.2 ±1.7	−1.5 ±1.8	− .1 ±1.3
C	7	0	+ 3.2 ±1.3	+ 2.4 ±2.3	+3.6 ±1.3	+1.2 ±1.6

The values given are the means plus or minus the probable error of the mean.

$$\text{mean} = \frac{\Sigma\left(\frac{S-C}{C} \times 100\right)}{n}; \quad \text{P.E.} = \frac{.6745}{\sqrt{n(n-1)}} \sqrt{\Sigma d^2}$$

where d = deviation from mean. Exp. 5 and 11 are not included in group A; in no. 5 the dry weight values were abnormally high, and in no. 11 the C nerve was lost.

Table 3. Changes in control nerves due to soaking

Hrs.	No. of cases	Mg. per cent K in wet nerve	Mg. per cent K in dry nerve	Mg. per cent in nerve water	Per cent dry weight	Cc. H_2O per 100 gm. dry
2–5	10	217.8 ±3	801.1 ±10.5	299.9 ±4.8	27.3 ± .4	268.3 ±4.9
25–100	10	207.5 ±3	816.7 ±14.4	279 ±4.7	25.5 ± .4	293.8 ±6.2
Av. per cent diff.		4.7 ±1.9	1.9 ±2.2	7 ±2.2	6.6 ±1.8	9.5 ±2.9

The values in the first two lines are means ±P.E. and in the third line the "Av. per cent diff." is the percentage difference of the above two means ±P.E. of the difference (P.E. diff. = $\sqrt{\text{P.E.}_1)^2 + (\text{P.E.}_2)^2}$). Exp. 5 and 11 are excluded from this table because of abnormal dry weights in the former, and loss of the C nerve in the latter. Exp. 26–29 provide 2 C nerves each.

2–5 hours at a calculated rate of 8–20 mg. per cent per hr., although the gain of water continued for a longer period. Fenn *et al.* (1934) reported that frog nerves soaked in a solution similar to ours and containing 8 mg. per cent of K lost 2–3 mg. per cent per hr. for 16 hr. which is equivalent to 8 mg. per cent per hr. for 5 hr. Cowan's (1934) estimate for unmyelinated crab nerves is 6–12 mg. per cent per hr. for 1 hr.

There is some divergence between the average K values of frog nerve as reported by us and by Fenn *et al.* Their figures were 188 ±17 mg. per cent in spring frogs, 118 ±10 in winter frogs. We found 211 ±2 in both

classes based on 35 controls, or 218 ± 3 in the 10 controls with the least soaking. The lowest value for any single control was 173 mg. per cent.

Action potential. On the average the figures of Table 1 show that the action potential decreased to 47 per cent of its initial value after long stimulation (Group A) and only to 82 per cent after short stimulation (Group B). This decrease was presumably due to the stimulation rather than to the soaking, since the potentials of the C nerves of the two groups did not decline during the experiments. The change in the S nerves may have been due to the loss of potassium which was measurable only in group A where the fall of action potential was marked. However, within group A there was no evident correlation between low action potentials and large losses of K. Low potentials rather go hand in hand with low temperatures. In 6 of the long run experiments (group A) the initial potential fell more than 50 per cent upon stimulation, and 5 of these cases were at approximately 15°C. The loss of K was the same in these 6 experiments (average 11–14 mgm. per cent) as in the other 4 experiments at about 25°C. In the short run trials (group B), only 3 cases were seen with a potential drop below 70 per cent of the original height, and all these were in the 15°C. range.

It might be argued that the decline of potential in active nerves was a sign of fatigue, or injury to some of the fibers. We excluded the possibility of injury, at least, by stimulating 5 different sets of nerves from 1–2.5 hr. each, and then allowing them to rest. The potentials, which had been reduced by an average of 50 per cent during stimulation, showed 90–100 per cent recovery after 30–60 min. of rest. Any injury which occurred therefore was reversible and not permanent.

Conclusions. These experiments provide definite evidence that even myelinated nerves in vitro do lose K with prolonged stimulation. Whether activity in vivo is ever sufficiently intense to permit this to occur in measurable amounts is a matter of conjecture, although Fenn failed to find evidence of it. Presumably there is a tendency to lose K during activity but normally the return must be practically completed during the refractory period.

When the circulation is intact, the conditions of diffusion might be more favorable for an exchange of K. Yet Rosenblueth and Luco (1939) stimulated cat nerves with an intact blood supply for as long as 5 hours without a fall in action potential, and hence presumably without a loss of K. This might indicate that diffusion of K is more rapid in vitro than in vivo.

Summary

1. Frog nerves immersed in Ringer's solution lose 11 per cent of their K (10–20 mg. per cent per hr.) during stimulation with 60 shocks per sec. over a period of 60–210 min. There is no significant change during stimulation for periods of 30 min. or less.

2. Stimulation causes no shift of water, judging from the constancy of the dry weight fractions of the nerves.

3. Soaking 2–5 hr. without stimulation causes a leak of K of approximately 8 mg. per cent per hour. No further movement of K occurs when soaking is continued to 25–100 hr.

4. Soaking 25–100 hr. increases the volume of nerve water by 9.5 per cent, thereby decreasing the dry weight fraction by 6.6 per cent, and the concentration of K in nerve water by 7 per cent.

We wish to thank Prof. W. O. Fenn for his suggestion of this problem, and his patient assistance. Dr. A. C. Young was kind enough to build our vacuum tube amplifier and to aid us with the problems of recording and stimulating.

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